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American Heart Journal

VOL. 36 September, 1948 No. 3

Original Communications

ANALYSIS OF MALFORMATIONS OF THE HEART AMENABLE TO A BLALOCK-TAUSSIG OPERATION

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THE operation developed by Dr. Alfred Blalock for the treatment of pulmonary stenosis and atresia is designed to increase the circulation to the lungs. Therefore, it should be of benefit to any person whose primary difficulty is lack of adequate pulmonary blood flow, provided the structure of the heart is such that it can adjust to the altered circulation.

Experience has shown that a patient with a tetralogy of Fallot can adjust to these changes in the circulation.

The main purpose of this paper is to analyze the findings of diagnostic significance in patients with other malformations which have proven amenable to this operation, and to give a brief summary of the long-time results following this operation.

Between July, 1945, and July, 1947, in addition to individuals with the tetralogy of Fallot, forty-seven patients have been operated on for the alleviation of pulmonary stenosis or atresia. This group was composed of patients whose cardiac contours were similar to those of a tetralogy of Fallot but with electrocardiographic evidence of a left axis deviation, patients with dextrocardia with or without situs inversus, patients with partial rotation of the heart upon its axis, patients whose clinical diagnosis was "pure" pulmonary stenosis with an auricular septal defect, and patients with unusual arrhythmias. The number of persons and the mortality rates in the respective groups are shown in Table I.

The George Brown Memorial Lecture delivered at the 20th Annual Scientific Meeting of the American Heart Association, Atlantic City, N. J., June 7, 1947.

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The overall mortality rate for the first 350 operations* on all patients of all ages with all types of malformations in which the clinical diagnosis was lack of adequate pulmonary blood flow was 19 per cent. Furthermore, in this series, among the children between 2 and 12 years of age with a tetralogy of Fallot on whom it was possible to use the subclavian artery, the operative mortality rate was less than 7 per cent. Table I shows that the operative risk is considerably greater in persons with the atypical malformations with pulmonary stenosis or atresia than in those with the tetralogy of Fallot.

Accurate diagnosis of these atypical malformations is extremely difficult. A person with a left axis deviation, with a dextrocardia with or without situs inversus, with an incomplete rotation of the heart on its axis, or with unusual arrhythmias presents an abnormality which is a definite specific entity. The only group in which the diagnosis is open to question is the group with "pure" pulmonary stenosis.

TABLE I. ATYPICAL MALFORMATIONS OF THE HEART WITH PULMONARY STENOSIS AND ATRESIA SUBMITTED TO A BLALOCK-TAUSSIG OPERATION

	NO.	DEATHS	MORTALITY
Malformation			
Left axis deviation	19	3	15%
Dextrocardia	12	4	33%
Slight rotation of heart	3	2	66%
"Pure" pulmonary stenosis	4	2	50%
Situs inversus with levocardia	3	1	33%
Abnormal rhythms			
Nodal rhythm	4	3	75%
Wolff-Parkinson-White syndrome	1	1	100%
Complete dissociation	1	0	0

The majority of patients whose cardiac contour is similar to that of a tetralogy of Fallot, but who present electrocardiographic evidence of a left axis deviation and left ventricular hypertrophy, suffer from defective development of the right ventricle combined with tricuspid atresia and pulmonary atresia. Those with a dextrocardia, with or without a situs inversus, and those with partial rotation of the heart comprise a variety of malformations, but of the abnormal location of the apex beat or of the abdominal organs there is no question.

The separation of malformations on the basis of arrhythmias may seem arbitrary. This is done because, in our experience, persons with a tetralogy of Fallot have a normal sinus mechanism and the occurrence of a nodal rhythm or of a Wolff-Parkinson-White syndrome is reason to doubt the diagnosis of a tetralogy of Fallot. Indeed, not one of the patients with an abnormal rhythm who died had a tetralogy of Fallot. Of the two who were improved by operation, the exact anatomic structure of the heart could not be established.

*In the subsequent 250 operations the mortality rate was less than 10 per cent.

The diagnosis of "pure" pulmonary stenosis, that is, a pulmonary stenosis without a ventricular septal defect, was based on the contour of the heart, the circulation time, physiologic studies, and cardiac catheterization. All four patients were severely incapacitated. It was hoped that the auricular septal defect would serve to direct venous blood from the right auricle to the left and thereby compensate for the lack of an over-riding aorta.*

Two of the patients in whom the diagnosis of "pure" pulmonary stenosis was made were improved by operation; the other two died. In one the diagnosis was confirmed at autopsy; in the other, the diagnosis was wrong. In the latter case autopsy revealed a tetralogy of Fallot with an aorta which over-rode the ventricular septum to such an extent that after operation there was difficulty in the expulsion of blood from the left ventricle; moreover, there was no auricular septal defect.

In order to determine the advisability of operation on a patient with any unusual malformation, attention is directed primarily to the criteria which have proved essential for the successful completion of the operation. There are six such criteria which must be met. (1) The primary difficulty must be lack of adequate pulmonary blood flow. (2) There must be a pulmonary artery to which the systemic artery can be anastomosed. (3) A systemic artery must be available to use for the anastomosis. (4) The difference in pressure between the systemic and the pulmonic circulations must be such that blood will flow from the aorta to the pulmonary artery. (5) The structure of the lungs must be such that the patient can survive the collapse of one lung and the occlusion of one pulmonary artery. (6) The structure of the heart must be such that it can adjust to the altered circulation.

The first two and the last two of these considerations are the primary concern of the cardiologist, as there is always a systemic artery and, provided the diagnosis is correct, the pulmonary pressure will be low. Errors in diagnosis have been made and high pulmonary pressure has been encountered. Consequently, this problem will be considered in detail in the differential diagnosis of lack of adequate pulmonary blood flow.

Lack of adequate pulmonary blood flow is indicated by various findings. The history may be of aid in that most of these children squat when tired. Clinical examination offers several clues. The purity of the second sound at the base is often significant. Reduplication of the second sound is in all probability caused by the asynchronous closure of the aortic and pulmonic valves and is, therefore, good evidence that both great vessels are of functional importance. Conversely, a pure second sound suggests that functionally there is but one great vessel. In the presence of pulmonary stenosis or atresia, so little blood reaches the lungs that, even with cardiac failure, pulmonary congestion rarely occurs. Indeed, pulmonary congestion is strong presumptive evidence of adequate pulmonary blood flow. For the same reason, the history of hemoptysis is always suggestive of excessive pulmonary blood flow. However, hemoptysis must be

*Recent experience has shown that a patient with "pure" pulmonary stenosis and an auricular septal defect may not be able to maintain compensation after operation.

differentiated from the bleeding caused by the rupture of dilated esophageal varices due to collateral circulation.

The existence of a pulmonary artery to which to anastomose the systemic artery is essential for the completion of the operation. This, however, may be impossible to determine with certainty prior to the thoracotomy. Various clues as to the existence of a pulmonary artery may be present. The persistent patency of the ductus arteriosus is clear evidence of the presence of a pulmonary artery. When a patent ductus arteriosus occurs in combination with pulmonary stenosis or pulmonary atresia, the continuous murmur of a patent ductus arteriosus is widely transmitted throughout both lungs and is well heard posteriorly both to the right and to the left. Such a murmur must, however, be differentiated from the continuous murmur which may result from collateral circulation. Usually the murmur of a patent ductus arteriosus is louder than that which results from collateral circulation and, in addition, there is a palpable thrill over the base of the heart. If the murmur is limited to one side of the chest, it is clear evidence that blood is directed only to one lung; hence, in all probability the circulation is not by way of the ductus arteriosus but is through a large vessel of the collateral circulation. Similarly, if the continuous murmur is audible only in a certain part of the chest, it is presumptive evidence that the murmur is due to collateral circulation. The continuous murmur indicates the continuous flow of blood to that lung; therefore, it is the opposite lung which is in greater need of increased circulation. Moreover, when the main pulmonary artery is absent, the entire circulation is necessarily through the pathways of collateral circulation. Such a patient may not be able to survive the collapse of the lung which has the better circulation. Consequently, if operation is to be attempted, it should be performed upon the side opposite to that over which the continuous murmur is audible.

Although Dr. Blalock has operated successfully on some patients believed to have a patent ductus arteriosus who also had reduced pulmonary blood flow, the accuracy of the diagnosis of a patent ductus arteriosus could not be verified because the operation was performed on the side opposite to that of the supposed ductus arteriosus. The other condition, namely, a continuous murmur originating from large vessels of collateral circulation in the absence of a pulmonary artery, has been verified at autopsy.

The density of the hilar shadows is of great importance. In infants with inadequate pulmonary blood flow, the lungs are exceptionally clear. In older children, if the collateral circulation develops by way of the posterior mediastinal vessels, the hilar shadows become exaggerated. Such shadows must be differentiated from those caused by large pulmonary vessels. A large pulmonary artery usually causes large blotchy shadows. Those caused by the minute vessels of collateral circulation are the result of an aggregation of innumerable small discrete shadows. Such shadows never show expansile pulsations. This single finding differentiates these shadows from those due to a large pulmonary artery in which there is high pulmonary pressure. The hilar shadows should also be evaluated in relation to the extent of the collateral circulation; the latter is

usually proportional to the polycythemia. Persons with a left axis deviation, however, frequently show denser hilar shadows than are seen with a tetralogy of Fallot and a corresponding degree of polycythemia. This is probably due to the fact that a left axis deviation is commonly associated with defective development of the right ventricle, tricuspid atresia, and pulmonary atresia; consequently, the development of collateral circulation is essential in order for the patient to survive the closure of the ductus arteriosus. The vast majority of children with a tetralogy of Fallot have pulmonary stenosis. It is only rarely that a patient with a tetralogy of Fallot and pulmonary atresia survives the closure of the ductus arteriosus. Consequently, the collateral circulation develops at a somewhat later age in a child with a tetralogy of Fallot and pulmonary stenosis than in a child with pulmonary atresia, and is correspondingly less extensive.

Special laboratory tests are of aid in doubtful cases. The most useful and and also the simplest of these is the exercise test developed by Dr. Richard Bing. Bing* has demonstrated that upon exercise patients with pulmonary stenosis or atresia show a fall in the oxygen consumption per liter of ventilation, whereas normal persons and most patients with a normally placed pulmonary artery (as, for example, an Eisenmenger complex) upon exercise show an increase in oxygen consumption per liter of ventilation. This simple test has proved of great help in the determination of reduction of pulmonary blood flow and in the differentiation of a tetralogy of Fallot from an Eisenmenger complex. The test does not, however, differentiate a tetralogy of Fallot from a complete transposition of the great vessels and should not have precedence over indubitable fluoroscopic evidence of increased pulmonary blood flow.

Angiocardiography may be of help in the visualization of the pulmonary artery. Failure to visualize the pulmonary artery does not, however, mean that the pulmonary artery is absent. In our experience in cases of extreme pulmonary stenosis, not infrequently too little radiopaque substance passes into the pulmonary artery to visualize it. Obviously, if there is atresia of the pulmonary orifice, no dye will pass into the pulmonary artery; nevertheless, in the majority of cases the pulmonary artery beyond the point of atresia, although small, is normally formed and can be used to direct blood to the lungs. In general the larger the aorta, the smaller is the pulmonary artery. Nevertheless, even in some instances of a truncus arteriosus in which the circulation to the lungs is by way of the bronchial arteries, there is a vestigial pulmonary artery which ends blindly but is of sufficient caliber to permit the anastomosis of a systemic artery to it. Therefore, in the last analysis it may not be possible to determine the existence and the size of the pulmonary artery without thoracotomy.

Catheterization of the heart is of great help in the determination of pulmonary stenosis when it is possible to catheterize the pulmonary artery and

*Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease. I. Procedures. II. Results of Preoperative Studies in Patient With Tetralogy of Fallot. Bull. Johns Hopkins Hosp. 80:107, 121, 1947. III. Results Obtained in Five Cases of Eisenmenger's Complex. Bull. Johns Hopkins Hosp. 80:323, 1947.

measure the pulmonary pressure. However, in the presence of pulmonary atresia this is manifestly impossible.

Nevertheless, if there is clear evidence that the primary difficulty is reduction in the pulmonary blood flow, exploratory operation is indicated, provided the evidence at hand indicates that the size and structure of the heart are such that it can adjust to the altered circulation.

There are four primary considerations in regard to the structure of the heart. First, venous blood must be directed to the systemic circulation; second, oxygenated blood must be able to reach the aorta; third, the structure must be such as to permit the continuous circulation of blood at an accelerated rate; and fourth, the cardiac reserve must be such that the heart can carry the increased load placed upon it by the altered circulation.

Some venous blood must be directed into the aorta, for it is the direction of the unoxygenated blood to the lungs which is of benefit to the patient. Indeed, the fundamental difference between the persistent patency of the ductus arteriousus as an isolated malformation and the creation of an artificial ductus in a tetralogy of Fallot is that in the former only fully oxygenated blood flows through the ductus arteriousus to the lungs, whereas in the latter the aorta overrides the ventricular septum and consequently some venous blood from the right ventricle is directed into the aorta and hence to the lungs for aeration. After operation, the oxygen saturation of the arterial blood rises to between 75 and 85 per cent but it never reaches 100 per cent. Furthermore, in most instances there is a fall in the oxygen saturation of the arterial blood with exercise; consequently, although at rest the oxygen saturation of the blood which is directed through the anastomosis to the lungs may be slightly higher than that of normal mixed venous blood, upon exercise the blood directed to the lungs is closely comparable to that directed to the lungs from the right ventricle in the normal heart.

An over-riding aorta or some other right-to-left shunt is essential for the direction of venous blood to the lungs. The over-riding of the aorta may, in doubtful cases, be determined by a number of methods. The simplest of these is the determination of the circulation time. An abnormally short circulation time, arm-to-tongue, of less than ten seconds is clear indication that venous blood has reached the aorta without passage through the lungs. In doubtful cases angiocardiography may be of great help by the early visualization of the aorta. Catheterization of the heart will also demonstrate the over-riding aorta, if the catheter passes directly from the right ventricle into the aorta.

In one child with a situs inversus and a levocardia, angiocardiograms revealed that a right superior vena cava opened into the right auricle and that a persistent left superior vena cava opened into the left auricle. The aorta arose entirely from the left ventricle. In this instance there was clinical and laboratory evidence of reduced pulmonary blood flow. Inasmuch as venous blood was directed to the aorta by way of the anomalous superior vena cava, it was believed that the patient would be benefited by operation. Such was the case. After operation the oxygen saturation rose from 67 per cent to 78 per cent and the red

blood cell count fell from 10 million to 5.2 million per cubic millimeter. Moreover, there was virtually no demonstrable change in the size of the heart.

The ease with which oxygenated blood from the left ventricle is directed to the aorta is determined by the size of the aorta and the degree of the dextroposition. Usually the aorta arises mainly from the left ventricle and only slightly over-rides the ventricular septum. Unfortunately, there are a few cases in which the aorta over-rides the ventricular septum to such an extent that, after operation, the left ventricle has been unable to expel the increased volume of blood which has been returned from the lungs to that chamber. Under such circumstances angiocardiography is of little aid, because in the presence of pulmonary stenosis so little dye reaches the lungs and the diffusion of the dye through the systemic circulation is so great that it is impossible to visualize the return of the dye to the left side of the heart. Catheterization of the heart gives little or no information concerning the left side of the heart. Consequently, this problem remains an enigma.

If there is a single ventricle, there is never any difficulty in the expulsion of the blood from the common chamber into the aorta. Furthermore, there will be complete admixture of oxygenated blood from the left auricle and venous blood from the right auricle in the common ventricle. In such a malformation the crucial factor is not the structure of the ventricle and its relation to the aorta, but the structure of the tricuspid valve and of the auricular septum and the severity of the pulmonary stenosis. If there is a gross defect in the auricular septum, no difficulty will be encountered in the direction of blood from either auricle to the ventricle. If, however, there is tricuspid atresia and only a small defect in the auricular septum, there may be difficulty in the expulsion of blood from the right auricle to the left.

The expulsion of blood from the right auricle becomes of great importance in cyanotic patients with a left axis deviation. On the basis of a limited number of autopsies, patients with a cardiac contour similar to that of a tetralogy of Fallot but with electrocardiographic evidence of left ventricular hypertrophy frequently have tricuspid atresia and defective development of the right ventricle; often the right ventricle is virtually a blind sac from the base of which the pulmonary artery takes its origin. Under such circumstances, the flow of blood is from the right auricle to the left auricle and thence to the left ventricle and out by way of the aorta. In all such malformations some defect in the auricular septum is inevitable. The defect may, however, be so small that there is difficulty in the expulsion of blood from the right auricle. The presence or absence of pulsations at the margin of the liver offers a valuable clue to the structure of the auricular septum. Pulsation at the margin of a liver of normal size is strong presumptive evidence of tricuspid stenosis or atresia combined with an opening in the auricular septum so small that there is difficulty in the expulsion of blood from the right auricle. In some instances, although before operation the defect in the auricular septum may have been sufficiently large to permit the expulsion of blood from the right auricle, with the increased minute output of the heart after operation this has no longer been possible, and the

patient has developed right-sided cardiac failure with a pulsating liver. Over a period of weeks most of these patients have adjusted to the load and have left the hospital improved; in two infants, however, the strain on the heart ultimately proved fatal.

A single ventricle is also relatively common in patients with persistent cyanosis who have a dextrocardia with or without situs inversus. In such malformations it is usual to find that both the mitral and the tricuspid valves or a common atrioventricular valve open into the common ventricle. Under such circumstances, it is the severity of the pulmonary stenosis which is of importance. It is essential for the pulmonary stenosis to be extreme because, inasmuch as both vessels arise from the same chamber, the stenosis of the pulmonary orifice is the principal mechanism which lowers the pressure in the pulmonary artery. The pulmonic pressure must be appreciably lower than the systemic pressure for blood to flow from the aorta to the lesser circulation. In two instances of a single ventricle in combination with a partial rotation of the heart, although the pulmonary artery was smaller than the aorta, the pulmonary pressure was relatively high; so high that the anastomosis did not continue to function. If, however, there is extreme pulmonary stenosis or pulmonary atresia and provided blood can flow from both auricles into the single ventricle, a single ventricle is quite as amenable to this operation as is a tetralogy of Fallot.

The cardiac reserve and the ability of the heart to adjust to the altered circulation are best demonstrated by the postoperative course.* The amount of cardiac enlargement which has occurred after operation has varied from patient to patient. The operation, however, has rarely led to progressive cardiac enlargement in patients with a tetralogy of Fallot. Indeed, of the first 220 patients operated on for pulmonary stenosis or atresia who were discharged improved, between February, 1945, and July, 1947, only three† are known to have died of cardiac failure. Two of these patients were infants who had electrocardiographic evidence of left axis deviation, in whom the clinical diagnosis was pulmonary atresia combined with tricuspid atresia and single ventricle. In one the diagnosis was confirmed at autopsy. In this instance, the auricular septum had only a small defect; the defect was so small that the heart was unable to maintain compensation after the rate of the circulation had been increased by the operation. The third death from cardiac failure was in a child with a spastic quadriplegia; autopsy was not permitted.

Although there have been only three deaths from cardiac failure, two other patients have developed cardiac failure and, in a number of instances, the operation has led to considerable cardiac enlargement. Great or progressive cardiac

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*Detailed follow-up studies are to be reported by R. Whittemore and H. B. Taussig.

†In addition to these three cases, there have been five other deaths. Three died suddenly. Autopsy was obtained in only one of these patients. In this instance there was an extensive medial sclerosis and a recent myocardial infarction. The second patient died suddenly several weeks after dental extraction; prior to dentistry she had received no prophylactic therapy and died while her jaw was swollen. The third died suddenly while convalescing from jaundice.

During the six-month interval, July, 1947, to December, 1947, two more children have died suddenly. One proved to have an unsuspected streptococcus meningitis and the other a thrombus in the left ventricle.

enlargement is clearly an unfavorable sign and, unless a balance is established, will ultimately cause death.

Fortunately, progressive cardiac enlargement has been rare. Indeed, only two or three patients of these first 220 patients followed for a period of more than two years have been known to continue to show increase in the size of the heart after the sixth postoperative month. It has been gratifying to find that in approximately 40 per cent of patients the operation has caused no demonstrable cardiac enlargement. Quite a number of patients (approximately 30 per cent) have developed cardiac enlargement during the first three weeks after operation but thereafter there has been no further cardiac enlargement. Almost an equal number of patients have shown an increase in the size of the heart between the time of discharge and their return for the six-month checkup; thereafter, the heart has adjusted to its load and there has been no further cardiac enlargement. The initial enlargement is undoubtedly caused by the increased load placed on the heart by the altered circulation. The enlargement which occurs between three weeks and six months after operation coincides with the period during which, for the first time, the patient has greatly increased his acitivity.

The degree of cardiac enlargement has varied from patient to patient. In general, there has been greater cardiac enlargement when the innominate artery has been used for the anastomosis than when the subclavian artery has been used, and the abnormally small hearts have shown greater cardiac enlargement than have the hearts which were at or above the upper limits of normal. Many of these patients with abnormally small hearts had extremely low basal metabolic rates. The operation caused prompt rise in the basal metabolic rate and a corresponding increase in the minute output of the heart. This may explain why many patients with very small hearts, which were associated with a low basal metabolic rate, have shown marked increase in the size of the heart postoperatively. In most of these patients the innominate artery was used for the anastomosis. Thus, a number of factors are involved: the altered circulation, the altered metabolic rate, the increased work demanded of the heart associated with the increased activity of the patient, and the size of the vessel used for the anastomosis. The relative importance of the various factors in the production of cardiac enlargement is under investigation. The objective is to place a minimal strain on the heart and to give adequate, not excessive, pulmonary blood flow.

All present evidence indicates that in the vast majority of instances adequate circulation to the lungs can be attained by the use of the subclavian artery. Table II illustrates how great an effect may be attained upon the oxygen saturation of the arterial blood and the polycythemia three weeks after an operation in which the subclavian artery has been anastomosed to the pulmonary artery. Table III shows the changes in the arterial oxygen saturation, the red blood cell count, and the hematocrit reading before and immediately after operation, and six months, one year, and two years after the anastomosis of the innominate artery to the pulmonary artery. Table IV shows similar determinations in a series of cases in which the subclavian artery was used for the anastomosis.

TABLE II. COMPARISON OF THE OXYGEN SATURATION OF THE ARTERIAL BLOOD, RED BLOOD CELL COUNT, HEMOGLOBIN, AND HEMATOCRIT BEFORE AND AFTER A BLALOCK-TAUSSIG OPERATION (SUBCLAVIAN ANASTOMOSIS)

NAME	OXYGEN SATURATION (%)		RBC (MILLIONS)		HGB. (GMS)		HCT. (MM.)	
	BEFORE OPERATION	AFTER OPERATION	BEFORE OPERATION	AFTER OPERATION	BEFORE OPERATION	AFTER OPERATION	BEFORE OPERATION	AFTER OPERATION
B. W.	56	83	9.7	5.9	29	15	73	47
G. W.	24	64	7.9	6.4	22	17	73	55
H. W.	24	80	7.3	4.7	—	14	64	41
M. F.	29	70	8.7	5.6	19	14	73	50
B. W.	36	82	9.7	5.9	—	—	73	47

TABLE III. THE EFFECT OF A BLALOCK-TAUSSIG OPERATION (INNOMINATE ANASTOMOSIS) ON THE ARTERIAL OXYGEN SATURATION, THE RED BLOOD CELL COUNT, AND THE HEMATOCRIT READING OF FIVE PATIENTS WHO HAVE BEEN FOLLOWED FOR TWO YEARS

	NAME	PRE-OP.	POST-OP.	6 MO.	1 YR.	2 YR.
	Arterial Oxygen Saturation (Per Cent Saturation)					
1	B. R.	36	82	86	84	—
2	J. S.	65.8	79	84	83	68
3	M. C.	20.6	47.9	58.9	59	64
4	J. R.	20.5	67.3	73	64	72
5	J. B.	46	75	79	87	81
	Red Blood Cell Count (Millions)					
1	B. R.	7.6	5.7	4.9	4.3	5.4
2	J. S.	9.0	6.9	5.3	5.0	4.8
3	M. C.	5.7	5.2	6.3	6.3	6.4
4	J. R.	9.1	6.2	5.3	4.8	5.9
5	J. B.	9.6	7.0	5.9	4.3	4.9
	Hematocrit Reading					
1	B. R.	57	46	—	47	48
2	J. S.	71	56	43	47	41
3	M. C.	45	42	48	47	53
4	J. R.	66	53	53	44	51
5	J. B.	84	48	37	42	42

Illustrative cases are given in all tables. In Table III it will be noted in Case 2 that although the last determination of the arterial oxygen saturation has fallen, the red blood cell count and the hematocrit reading have not increased. Therefore, it is hoped that the fall in oxygen saturation of the arterial blood was due to the fact that the patient was crying when the sample was taken. A

TABLE IV. THE EFFECT OF A BLALOCK-TAUSSIG OPERATION (SUBCLAVIAN ANASTOMOSIS) ON THE ARTERIAL OXYGEN SATURATION, THE RED BLOOD CELL COUNT, AND THE HEMATOCRIT READING ON FIVE PATIENTS WITH PULMONARY STENOSIS OR ATRESIA

	NAME	PRE-OP.	POST-OP.	6 MO.	1 YR.	2 YR.
			Arterial Oxygen Saturation (Per Cent Saturation)			
6	R. S.	78	85	86	88	88
7	H. G.	65	81	82	—	83
8	H. O.	59	77	76	—	71
9	M. S.	49	68	78	77	81
10	P. R.	47	67	7	78	76
			Red Blood Cell Count (Millions)			
6	R. S.	6.4	5.5	5.5	5.5	5.5
7	H. G.	10.5	6.6	5.5	5.0	4.8
8	H. O.	6.3	5.6	4.4	6.0	6.1
9	M. S.	6.6	4.7	5.4	5.5	5.3
10	P. R.	9.8	6.6	7.8	5.5	5.5
			Hematocrit Reading			
6	R. S.	59	48	41	46	46
7	H. G.	86	56	47	—	47
8	H. O.	59	49	41	—	51
9	M. S.	64	51	54	54	51
10	P. R.	68	56	58	51	46

similar fall was noted in Case 4 in the sample taken at one year of age. In Case 3, although the oxygen saturation has risen steadily, the red blood cell count has also risen. This patient was an infant. At the time of operation, as so frequently occurs in early infancy, there was no compensatory polycythemia. The arterial oxygen saturation, although it has risen markedly, has only just reached 64 per cent. It is hoped that it may rise still further, and that when it reaches 75 to 80 per cent, the red blood cell count will again decline. Obviously the combination of a red blood cell count of 6 million and an arterial oxygen saturation of 64 per cent is better than that of a red blood cell count of 5 million and an arterial oxygen saturation of 20 per cent.

In Table IV, Case 8, the red blood cell count fell after operation but has subsequently risen to the preoperative level, and the arterial oxygen saturation has fallen slightly. This child had an unusually small subclavian artery and it is possible that the orifice of the anastomosis may not be increasing in size in proportion to the growth of the child. In the future, this child may require another operation. Two infants have already required a second operation.

In addition to these two, two other patients have had a recurrence of cyanosis and one has again developed polycythemia.

The one other unfavorable complication which we have encountered is subacute bacterial endocarditis. One child* has had and has been cured of subacute bacterial endocarditis.

In brief: the follow-up studies indicate that in most children the anastomosis of the subclavian artery to the pulmonary artery has been virtually as beneficial as has the innominate artery and that the load placed on the heart has not been as great. The oxygen saturation of the arterial blood has risen to between 70 per cent and 80 per cent, and the red blood cell count, the level of the available hemoglobin, and the hematocrit reading have returned to normal values. In the vast majority of instances the children have to date maintained this improvement.

SUMMARY

The Blalock-Taussig operation is of benefit to any patient who suffers from lack of adequate pulmonary blood flow, provided the structure of the heart is such that it is able to adjust to the altered circulation.

Experience has shown that a patient with a tetralogy of Fallot can adjust to the altered circulation. The other types of malformation which have been improved by operation are those with a cardiac contour similar to that of a tetralogy of Fallot with left axis deviation, those with partial rotation of the heart on its axis, possibly those with "pure" pulmonary stenosis and an auricular septal defect, and a few with unusual arrhythmias. In atypical cases an effort is made to determine whether the condition is such that the patient can be helped by increasing the circulation to the lungs.

The six criteria essential for successful operation are (1) the primary difficulty must be lack of adequate pulmonary blood flow; (2) there must be a pulmonary artery to which to anastomose the systemic artery; (3) a systemic artery must be available for the anastomosis; (4) the difference in pressure between the systemic and pulmonic circulations must be sufficiently great for blood to flow from the aorta to the lungs; (5) the structure of the lungs must be such that the patient can tolerate the collapse of one lung and the temporary occlusion of one pulmonary artery; and (6) the structure of the heart must be such that it can adjust to the altered circulation. The methods for the determination of each of these factors are discussed.

In an analysis of the structure of the heart it is emphasized that (1) venous blood must be directed to the systemic circulation, (2) the increased volume of oxygenated blood which is returned from the lungs must be able to reach the aorta; (3) the structure of the heart must be such as to permit the continuous circulation of the blood at an accelerated rate; (4) the structure of the heart must also be such that the operation does not cause progressive cardiac enlargement. Each of these factors is analyzed.

The effect of the altered circulation on the size of the heart is discussed in the light of the long-time results of the operation. Less than 5 per cent of the patients have shown progressive cardiac enlargement or died of cardiac failure.

*Since this paper was given seven other children have developed endocarditis. Five have been cured, one is still under treatment, and from one we have no report.

Thirty per cent have shown no increase in heart size. Thirty per cent have shown increase in heart size during the first three weeks after operation and then have adjusted to the load, and 30 per cent have shown cardiac enlargement between the time of discharge and the six-month checkup and thereafter have shown no further increase in heart size.

In general, the results from the use of the subclavian artery, as estimated by the oxygen saturation of the arterial blood, the red blood cell count, and the hemoglobin level, have been as beneficial as when the innominate artery has been used for the anastomosis and, moreover, this former group of patients has shown less increase in the size of the heart.

A child with a tetralogy of allot has a 90 per cent chance of being greatly improved by the operation and an equally good chance of maintaining that improvement.

CORONARY ARTERY DISEASE IN MEN EIGHTEEN TO THIRTY-NINE YEARS OF AGE

Report of Eight Hundred Sixty-Six Cases, Four Hundred Fifty With Necropsy Examinations*

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INTRODUCTION

PRIOR to World War II, coronary artery disease in men under 30 years of age was regarded as rare, and in men between 30 and 40 years of age, as uncommon. The present report of 866 cases in men between the ages of 18 and 39 years, inclusive, was made possible by the concentration of pathologic material from the Army during the war period at the Army Institute of Pathology and by the centralization of records of disabled veterans at the Veterans Administration Headquarters, both in Washington, D. C. In 450 cases,** the diagnosis was established by necropsy, and in 400 cases,*** the patients survived typical attacks of acute myocardial infarction. Actually 416 cases in the Veterans Administration were studied; but sixteen of these patients**** died subsequently, and although the diagnosis was also verified by necropsy in five, the necropsy records of these cases are not included in this report. Additional cases were still being reported after the series used in this report had been concluded, Sept. 1, 1946. Furthermore, the cases of many living patients were excluded because of inadequate data or atypical features, and many protocols were discarded because of inadequate clinical or pathologic data or insufficient pathologic material for study. The clinical data were considered satisfactory, and the tissues and sections available were sufficient for verification in all fatal cases included

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**Hereafter called "fatal cases."

***Hereafter called the "survivors." These were all men who served in the Army.

****Hereafter called "sixteen additional cases." These were all men who served in the Army.

in this series. Only those cases were accepted in which there was advanced coronary artery sclerosis and no other adequate cause of death. Thirty-seven of the fatal cases were reported before September, 1940, when the National Guard was mobilized; the remainder were accumulated after that date. All of the cases of survival of a typical attack of acute myocardial infarction were observed after Dec. 7, 1941.

REVIEW OF LITERATURE ON CORONARY ARTERY DISEASE IN PERSONS UNDER FORTY YEARS OF AGE

An extensive review of the literature has been made to determine the reported incidence of coronary artery disease in persons under 40 years of age. Several historical facts influence the results. Disease of the coronary arteries has been recognized for many years, but prior to the twentieth century little if any attempt at ante-mortem diagnosis was made, because it was generally regarded as of interest primarily to pathologists. Wolff and White,[1] writing in 1926, ascribed an ante-mortem diagnosis of coronary artery disease to Jenner and Parry in the eighteenth century and stated that the diagnosis was proved at necropsy.

The first description of the clinical picture of occlusion of a coronary artery is generally credited to Obrastzow and Straschesko[2] on the basis of their article which appeared in 1910. In America, Herrick's[3] original contribution on the subject appeared in 1912 and since then has been accorded the place of honor in American writings on coronary artery disease. It is interesting that in this article Herrick referred to two cases occurring in men under 40 years of age. His reference to Chiari's case has not been identified, but the other case, that of Merkel,[4] appears to be an authentic instance of coronary artery occlusion in a man 37 years of age. This case was one of aortic insufficiency, probably of syphilitic origin, in which, in addition to the aortitis, there were marked sclerotic changes in both right and left coronary arteries, the left being completely occluded. Because of the associated pathologic conditions, this case is not included in our tabulation.

The older literature deals largely with the subject of angina pectoris, although without doubt many of the cases were, in fact, coronary artery disease. Huchard,[5] in 1899, presented a large series of cases with briefs from 185 autopsies, most of which he had collected from the literature. In this group there were twenty-nine patients under the age of 40 years. Study of the autopsy briefs leads one to believe that the nature of the disease in many of the cases presented was syphilitic aortitis with secondary involvement of the coronary orifices. A number of others were undoubtedly due to rheumatic valvular lesions. However, careful scrutiny of Huchard's material indicates that nearly one-half of the cases in which the age was less than 40 years may have been instances of coronary artery sclerosis. Since in many of these cases microscopic descriptions are lacking and the data are incomplete, they have not been included in the accompanying tabulation. Mackenzie,[6] in his treatise on angina pectoris, included in an appendix a total of 160 case reports. There are twenty cases involving patients under the age of 40, and four of the twenty appear to be instances of

REPORTS IN LITERATURE OF PATIENTS UNDER FORTY YEARS OF AGE WITH CORONARY ARTERY DISEASE

AUTHORS	NUMBER UNDER 20 YR.	AGE	SEX	NUMBER BETWEEN 20 AND 29 YR.	SEX	TOTAL UNDER 40 YR.	SEX
Dreschfeld[16]	1	12	M			1	M
Wild[17]	1	12	F			1	F
Gilford[18]	1	18	M			1	M
Vaquez[19]	1	18	F			1	F
Benda[20]	1	13	F			1	F
Jamison and Hauser[21]	1	18	M			1	M
Barnes and Ball[22]	1	Under 20	?			?	?
Boas and Donner[23]	1	Between 11 and 20	M			12	M
Meakins and Eakin[24]	1	Under 19	M			7	M (6) F (1)
Sprague and Orgain[25]	2	Both 15	M			2	M
May[26]	1	19	?			4	?
Zacks[27]	1	19	M			1	M
Jokl and Greenstein[28]	1	10	M			1	M
Hughes (Osler's)[29]						1	M
Palmer[30]						1	M
Klingmann[31]						1	M
Levine and Tranter[32]						1	M
Wearn[33]						1	M
Nathanson[34]						2	?
Christian[35]						5	?
Krumbhaar and Crowell[36]						1	M
Clark[37]						1	M
Kerr and Larkey[38]						2	M
Allan[39]						1	M
Parkinson and Bedford[40]						4	?
Bramwell[41]						2	M
Conner and Holt[42]						20	?
Root and Graybiel[43]						2	M (1) ? (1)
Levy[44]						2	M (1) F (1)
Smith and Bartels[7]						2	M (1)
Lisa and Ring[45]				1	F	3	F (2) ?
Howard[46]						12	M
Riesman and Harris[47]						1	?
Leary[48]				3	M	10	M (9) F (1)
Coelho[49]						1	M
Rathe[50]						1	F
Horine and Weiss[51]						1	M
Cooley[52]						1	M
Fernando[53]				1	M	1	M
White[8]				4	M	14	M
Appelbaum and Nicholson[54]						3	?
Moritz and Beck[55]						5	?
Cooksey[56]						1	M
Mullins[57]				1	M	24	M (18) F (6)
Wright-Smith[58]				1	M	8	M (1) ? (7)
Master, Jaffe, and Dack[59]						21	M (15) F (6)
Willius[60]						6	M
White, Glendy, and Gustafson[61]				1	F	1	F

REPORTS IN LITERATURE OF PATIENTS UNDER FORTY YEARS OF AGE WITH CORONARY ARTERY DISEASE—CONT'd

AUTHORS	NUMBER UNDER 20 YR.	AGE	SEX	NUMBER BETWEEN 20 AND 29 YR.	SEX	TOTAL UNDER 40 YR.	SEX
Glendy, Levine, and White[62]						100	M (96) F (4)
Bean[63]				2	?	10	?
Benson[64]						1	M
Blaze[65]				1	M	1	M
Durant[9]				1	M	6	M
Franklin[10]						1	M
Sampson and Eliaser[66]						3	M (2) F (1)
Halbersleben[67]				1	F	1	F
Scott[11]				1	M	1	M
Goodson, Jr., and Willius[68]				3	?	30	M (24) F (6)
Ferguson and Lockwood[12]				1	M	1	M
Master, Dack, and Jaffe[69]				10	?	39	?
Jokl and Melzer[70]						2	M
Pollard and Harvill[71]						3	M (2) F (1)
Dawber[72]				1	M	1	M
Macdonald[73]				1	M	1	M
Clawson[74]				4	M	23	M (22) F (1)
Reitman, Greenwood, and Kler[13]				1	M	1	M
Smith, Sauls, and Ballew[75]				1	?	5	?
Garvin[76]						6	?
Miller and Woods[14]				1	M	1	M
Weinstein[77]				6	M	10	M
Shallenberger and Smith[78]						1	M
Master, Jaffe, Dack, and Grishman[79]						2	M (1) F (1)
Levan[80]						2	M
Donoso[81]				1	M	1	M
Nay and Barnes[82]						2	?
Kugel[83]				1	M	1	M
Meesen[84]				78	M	326	M
Tullis[85]				1	M	1	M

Total number patients less than 20 years		14
Males	9	
Females	3	
Sex not stated	2	
Total number patients between 20 and 29 years		128
Males	109	
Females	3	
Sex not stated	16	
Total number patients less than 40 years exclusive of 37 cases believed to be reported twice		744
Males	597	
Females	29	
Sex not stated	118	

sclerotic disease of the coronary arteries in young persons. These twenty cases have also been excluded from this tabulation.

In recent years, a number of reviews of the literature on coronary artery disease in younger individuals have served to focus attention on the subject. In 1932, Smith and Bartels[7] collected twenty cases which they believed to be proved coronary artery thrombosis occurring in patients under 40 years of age. To this group they added two cases of their own. In 1935, White[8] reviewed the literature, and although he did not attempt a tabulation of all cases, he did review much of the writing up to that date. In this same article, White added fourteen cases of patients under 40, including four of patients between the ages of 20 and 29 years. In 1937, Durant[9] briefly reviewed the literature, adding seven cases from his own material. In 1938, Franklin[10] added another case, and in the same year, Scott,[11] reporting the case of a 27-year-old man, reviewed the literature and stated that he had found records of 218 cases of coronary artery disease in patients under 40 years of age. A year later, Ferguson and Lockwood[12] added another case with a further review. In 1942, Reitman, Greenwood, and Kler[13] wrote that they had been able to find reports of 221 cases of coronary artery thrombosis occurring in patients under the age of 40 years. In this group, thirty-four patients were under 30, and four, under 20 years of age. The case presented by these authors was that of a 20-year-old man who had experienced a nonfatal attack. In 1943, Miller and Woods[14] reviewed the subject and added a case of a 22-year-old man who had suffered from coronary artery thrombosis with myocardial infarction. They presented in detail eleven cases from the literature, all of which occurred in patients 30 years of age or younger.

The present survey is intended to bring together these various reports and to add to them such cases as we have been able to collect. In tabulation of material from widely scattered sources, the possibility of duplicate reporting arises, and in an attempt to avoid this, certain series have been omitted when it appeared that the material had already been covered in other reports by the same authors. Even so, it is probable that a few cases may have been reported twice. On the other hand, in deleting several series, we have undoubtedly failed to report several bona fide cases. A second difficulty encountered in a survey such as this is that of language. For many years the literature on disease of the coronary arteries has been predominantly American, and, when to the American contributions are added those from other English-speaking countries, a large portion of the literature is accounted for. Today there is a growing world-wide interest in this subject, and the foreign literature is increasing. Only a small number of reports from the foreign literature have been included in the present review, which admittedly is deficient in this respect.

Notwithstanding the limitations just mentioned, we have been able to collect an imposing number of reports of cases of coronary artery disease occurring in individuals less than 40 years of age. Because much of the terminology in the literature is inexact, with coronary artery occlusion, coronary artery thrombosis, and myocardial infarction often being employed as synonyms, we have used the general term "coronary artery disease," and we have not attempted to separate

the reported cases into the various forms of the disease. We have employed the term to designate all atherosclerotic occlusive disease of the coronary arteries, with or without myocardial infarction.

The following list of seventy-eight references concerns a total of 781 patients less than 40 years of age who suffered from coronary artery disease. Notably omitted is the series of eighty cases of fatal coronary sclerosis reported by French and Dock[15] in 1944, because these cases are included in the main body of this study. It should be noted that Meesen's article[84] published in 1944 was apparently the German experience with coronary artery disease among soldiers in World War II.

Several figures should be subtracted from the totals. The series of Goodson and Willius includes one case previously reported by Smith and Bartels. The series of 100 cases reported by Glendy, Levine, and White undoubtedly includes the fourteen cases previously reported by White in 1935 and the one case reported by White, Glendy, and Gustafson in 1937. It is probable that the twenty-one cases reported by Master, Jaffe, and Dack in 1936 are included in the series reported by the same authors in 1939. Altogether this would make thirty-seven cases to be subtracted from the 781, leaving a total of 744 cases of coronary artery disease reported in individuals less than 40 years of age. The thirty-seven cases which we have subtracted from the total are shown in the list because in several instances they give data on the group of patients 20 to 29 years of age which are lacking in the larger series. The inclusion of these cases does not give rise to duplication in the totals of the 20- to 29-year group, however. The list shows that 128 cases have been reported in this age group. The group of those less than 20 years of age includes fourteen patients, the youngest of whom appears to be a 10-year-old boy whose case was reported by Jokl and Greenstein in 1944.

The sex incidence in the groups reported is of interest. The sex of twelve patients less than 20 years of age was reported; nine were of the male and three of the female sex. Of 112 of the patients 20 to 29 years of age, 109 were men and three were women. Of the 744 less than 40 years of age, the sex was specified in 626 cases, being male in 597 and female in twenty-nine. This would indicate a sex ratio of 95 per cent male to 5 per cent female in the entire group under 40 years of age. The sex ratio in the age group of 20 to 29 years would be 97 per cent male to 3 per cent female, whereas in the group under 20, it would be 75 per cent male to 25 per cent female.

ETIOLOGICAL CONSIDERATIONS

Regarding etiology, many factors were investigated in the series we are reporting. Since so many of the 450 men who died in apparent good health died so suddenly that accurate histories could not be obtained from them, questionnaires were sent to the "nearest of kin." In the cases of the 416 men who survived a typical attack of myocardial infarction in the Army, the histories as obtained from the men themselves were utilized. Control groups were used in both categories.

Because of difficulty in obtaining the addresses of some of the persons to whom it was desired to send questionnaires, the final number sent was 291. Copies of the questionnaire were also sent to 213 families of men who died of gunshot wounds. Of the former, only ninety-four questionnaires were answered and twenty-five came back because of wrong addresses, a return of 35 per cent. Of the 213 control questionnaires, sixty-two were answered and eleven came back because of wrong addresses, a return of 31 per cent. The main reason for the low rate of returns was probably the length of the questionnaire, which covered a wide range of information.

There was significant evidence found for a greater familial tendency toward heart disease among the relatives of the patients with heart disease as compared with the control group: 77 per cent for the former as compared with 53 per cent for the latter. For members of the immediate family, the percentages were 51 and 30, respectively. This difference was even greater between the men who survived an attack of myocardial infarction and a control group of 210 amputees and men hospitalized because of gunshot wounds. Hypertension and/or coronary artery disease occurred in the immediate family of the former in 41 per cent and in the immediate family of the latter in only 13 per cent. Thus, it appears that heredity may be an important factor in the development of coronary artery disease in the age group studied.

Other questions asked related to the type of birth, the condition of the mother during pregnancy, the economic status of the family during the childhood of the man, the number of children in the family, the age when walking began, eating habits, illnesses, smoking and drinking habits, temperament, athletic pursuits, occupational history, education, and marital life. Information from the questionnaires brought out the following comparisons in the two groups:

1. Men in the heart disease group were more likely to have a family history of heart disease.
2. The percentage of men of the heart disease group whose mothers were in good condition during pregnancy was slightly higher.
3. Eighty-one per cent of the men of the heart disease group, as compared with 63 per cent of the control group, were reported to be members of middle class families; the remainder of both groups were from poor families.
4. Relatively twice as many who died from heart disease began to walk before 17 months of age.
5. No important differences were apparent in the eating habits of the men in the two groups.
6. The percentage of patients known to have smoked five or more cigarettes daily was 53 per cent for the heart disease group and 57 per cent for the control group, a minor difference. The percentages of those who smoked more than ten cigarettes were, respectively, 68 and 19 in the two groups, which is more striking, and perhaps a more sensitive measure of the differences between the two groups.
7. The percentage of men who began drinking alcoholic beverages before the age of 20 years was slightly higher for the control group. No excessive drinkers were reported for the control group and only six for the heart disease group. Fifty per cent of the patients with heart disease drank.

8. Patients in the heart disease group were somewhat more likely to display nervous and anxiety traits 50 per cent or more of the time than the men in the control group, the percentages being 26 as compared with 16.

9. Relatively more patients in the group with heart disease had been engaged in light or moderately heavy work before entering the Army than had those in the control group. Only 20 per cent in the former group had held jobs involving heavy work, in contrast to 40 per cent in the latter group.

10. Relatively more patients in the heart disease group than in the control group had histories of "pneumonia and pleurisy" (21 per cent as against 9 per cent), "appendicitis" (17 per cent as against 5 per cent), "high blood pressure" (14 per cent as against 3 per cent), "heart trouble" (9 per cent as against 2 per cent), "kidney trouble" (5 per cent as against 0 per cent), and "leaky valve or murmur" (4 per cent as against 2 per cent). The percentages for the ordinary childhood diseases and others differed little in the two groups.

11. Shortness of breath as a frequent complaint was present in 12 per cent of men in both groups. Pain in the chest was often complained of by 16 per cent of patients in the heart disease group, as compared with 8 per cent of the control group. "Indigestion" was a frequent complaint of 22 per cent of patients in the heart disease group and 11 per cent of those in the control group.

The results of the analysis of the questionnaires are given only because they are of interest; the number of cases in both groups is too small to make them significant. The data obtained directly from 392 men who survived an attack of myocardial infarction and from 210 men suffering from traumatic conditions are of greater significance. Here, as we have already stated, hypertension and/or coronary artery disease was about four times as common in immediate members of the family (father, mother, brothers, and sisters) of the patients with heart disease as in the control group. In regard to the use of tobacco, differences between the two groups were not significant. Twelve per cent of the heart disease group denied the use of tobacco, as against 18 per cent of the control group. The respective percentages for those in the two groups who smoked fewer than twenty cigarettes a day were 17 and 14; between twenty and thirty-nine cigarettes a day, 60 and 62; and more than forty cigarettes a day, 11 and 6 per cent. There was, likewise, no significant difference in the two groups in the use of alcohol: In the heart disease group, 22 per cent denied the use of alcohol, 41 per cent admitted only occasional use of alcohol, 30 per cent admitted moderate use, and 7 per cent admitted heavy use. In the control group, 26 per cent did not use alcohol, 31 per cent drank occasionally, 41 per cent drank moderately, and 3 per cent admitted drinking heavily. The estimated degree of the use of alcohol was based on the opinion of the medical officer who questioned the patient, not on any fixed amount of alcohol consumed.

Age.—Table I gives the distribution of 849 men by age,* both in absolute numbers and percentage by years of age, and as compared with the percentage of men of similar ages in the entire Army. The table shows that sixty-four of the men were between 18 to 24 years of age, inclusive; 139 were 25 to 29 years,

*The exact age of one man was not given, but it was known definitely that he was less than 40 years of age.

inclusive; 266 were 30 to 34 years, inclusive; and 380 were 35 to 39 years of age, inclusive. The number having heart disease per 100,000 soldiers of that age rose sharply with advancing years as shown graphically in Chart I, where it is seen that death from coronary artery disease or myocardial infarction was forty times as common in men 35 to 39 years, inclusive, as in those whose ages were 18 to 24 years, inclusive. Presumably, at the time of induction, all, or at least most, of the 850 men were thought to possess normal cardiovascular systems, because they were accepted for service and, even at the time of death or acute myocardial infarction, were assigned to general Army duty.

TABLE I. AGE DISTRIBUTION OF MEN 18 TO 39 YEARS, INCLUSIVE, WITH CORONARY DISEASE COMPARED WITH THAT OF THE ARMY AND OF VETERANS RECEIVING DISABILITY PENSION AWARDS

AGE (YR.)	MEN WITH CORONARY DISEASE						ENTIRE ARMY* (PER CENT)	DISABLED VETERANS† (PER CENT)
	FATAL CASES		SURVIVORS		TOTAL			
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT		
18	1	0.2	0	0.0	1	0.1	3.7	0.1
19	0	0.0	0	0.0	0	0.0	5.2	1.1
20	2	0.4	5	1.2	7	0.8	6.1	3.3
21	4	0.9	2	0.5	6	0.7	7.6	4.9
22	13	2.9	7	1.8	20	2.4	8.0	5.6
23	12	2.7	4	1.0	16	1.9	8.0	6.9
24	10	2.2	4	1.0	14	1.6	8.0	7.5
25	15	3.3	7	1.8	22	2.6	7.2	7.1
26	16	3.6	7	1.8	23	2.7	6.6	7.1
27	18	4.0	11	2.8	29	3.4	6.2	6.9
28	11	2.4	12	3.0	23	2.7	5.4	5.8
29	18	4.0	24	6.0	42	5.0	4.8	5.4
30	27	6.0	25	6.2	52	6.1	4.2	4.8
31	21	4.7	17	4.3	38	4.5	3.6	4.7
32	31	6.9	26	6.5	57	6.7	3.1	4.3
33	29	6.5	25	6.2	54	6.4	3.0	4.1
34	34	7.6	31	7.8	65	7.7	2.4	3.7
35	42	9.4	37	9.2	79	9.3	1.8	3.7
36	36	8.0	45	11.2	81	9.5	1.5	3.4
37	36	8.0	46	11.5	82	9.7	1.3	3.3
38	43	9.6	48	12.0	91	10.7	0.8	3.3
39	30	6.7	17	4.2	47	5.5	0.5	3.0
Total	450‡	100.0	400	100.0	850	100.0	100.0	100.0

*Based on data from War Department AGO Machine Records.

†Data from Veterans Administration, Budget and Statistics Division, on veterans who were receiving disability pension awards as of June 30, 1945.

‡Total includes one patient whose age was not definitely stated but was known to be under 40 years.

The number of men who died of coronary artery disease in relation to the size of the Army is rather small, the average during the war years having been 1.5 per 100,000 men per year. The average age of soldiers 18 to 39 years, inclusive, who died suddenly of coronary artery disease was 32.6 years. This may be com-

pared with the average age of 26.0 years for all men in the Army on Sept. 30, 1945 (a very small percentage of Army personnel was above 39 years of age). It is apparent that the men who died from coronary artery disease represent an older group than the average of the Army. Thus, there was only one death from this cause in soldiers below the age of 20 years, although 9 per cent of the men in the Army were under the age of 20 years. In addition, there was a steady rise in coronary deaths with increasing age, the mortality rate in the age group of thirty-five to thirty-nine years, inclusive, having been 12.2 cases per 100,000 men per year, whereas among the group 20 to 24 years of age, inclusive, the rate was only 0.4 per 100,000 men per year.

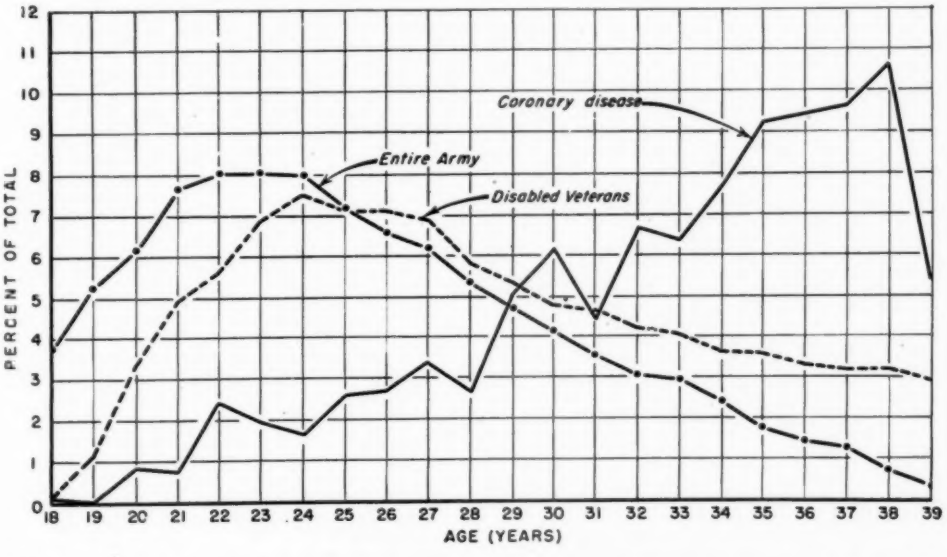

Chart 1.—Age distribution of men 18 to 39 years of age with coronary disease compared with that of the Army and of veterans receiving disability pension awards.

In the group of 400 World War II veterans 20 to 39 years of age, inclusive, who survived an attack of typical acute myocardial infarction, the average age was 33.0 years at the time of the "attack." The average age of the 537,084 veterans of World War II on the service-connected disability rolls as of June 30, 1945, was 29.4 years, with an age range of 16 to 69 years. It may be of interest to note that there were 1,710 veterans less than 40 years of age on the World War II pension rolls as of Dec. 31, 1945, whose disability was diagnosed as the result of coronary artery disease or angina pectoris, and 1,785 veterans 40 to 69 years of age, inclusive, on the pension rolls as of the same date with those diagnoses. The average age of these 3,495 men with coronary artery heart disease was 40.5 years, with an age range of 18 to 67 years.

Between the group of men who died suddenly and those who survived a typical attack of acute myocardial infarction, there is no significant difference with regard to the age factor. There was no indication of any correlation between

the age of the patient and the presence or absence of simple narrowing of the coronary arteries, occlusion (sclerotic alone, thrombotic alone, or both), gross myocardial infarction, or scars of the myocardium in the 450 fatal cases with autopsy.

Race.—There has been considerable discussion in medical literature regarding the incidence of coronary artery disease, acute myocardial infarction, and angina pectoris among Negroes and the differences in the clinical manifestations of the conditions in Caucasians and Negroes. Stone and Vanzant,[86] in a clinical study in 1927, found that arteriosclerotic heart disease was four times as common in white subjects as in Negroes. Schwab and Schultze,[87,88] in 1931 and 1932, arrived at the opinion that it was two and one-half times as common in white subjects. Lisa and Ring,[45] in 1932, found more than four times as many Caucasians as Negroes in 100 cases studied at necropsy. In 1933, Gager and Dunn[89] found twice as many white subjects as Negroes with this disease in a statistical study in Washington, D. C. In a study of necropsy material in the same city in 1935, Hedley[90] came to the conclusion that coronary arteriosclerosis and thrombosis are uncommon among Negroes. Johnston[91] in 1936 found a much greater incidence in white persons. In reports by Bruenn, Turner, and Levy[92] and by Levy and Bruenn,[93] in 1936, the ratio was twelve to one. In Bean's[63] report, in 1937, there were only sixteen Negroes in 300 cases examined at necropsy. Weiss,[94] in 1940, stated that coronary artery occlusion is rare in the Negro in the absence of hypertension. Smith, Sauls, and Ballew,[75] in 1942, reported an incidence of only 0.63 per cent of Negroes with coronary artery occlusion in 2,204 patients of all races with cardiac disease. On the other hand, Holoubek,[95] in 1945, found the ratio of white to Negro patients dying of arteriosclerotic heart disease to be 59 to 41. Fitzgerald and Yater,[96] in 1946, found thirty-five cases of myocardial infarction in Caucasians and the same number in Negroes in the autopsy material for a five-year period at the Gallinger Municipal Hospital, Washington, D. C. In that same period there were twice as many Negroes as white persons hospitalized in that institution, which may indicate that the incidence of myocardial infarction in Negroes is about 50 per cent of that in white persons, the Negroes showing a tendency to die of this disease about a decade earlier in life. Hunter,[97] in 1946, found sixteen Negroes and twenty-six white persons with coronary artery occlusion as the immediate cause of death in a series of 1,000 consecutive autopsies, the Negroes being younger and not suffering the pain so characteristic of the disease in the white race.

Among the 850 men in this series there were 784 Caucasians, 63 Negroes, 1 Filipino, 1 Mexican, and 1 Chinese (Table II). Since only 10 per cent of the men in the Army were Negroes, the incidence of coronary artery disease in the Negroes was somewhat more than two-thirds of that in the white soldiers. The incidence among Negroes was somewhat lower in the group that died than in the group that survived. The average age of the Negroes at the time of death in the fatal series was 32.1 years, and at the time of attack, among those who survived, it was 32.4 years, which clearly indicates that the age factor is not responsible for the somewhat less frequent occurrence of this type of death in Negroes.

TABLE II. RACE DISTRIBUTION OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE AND OF ALL MEN IN THE ARMY

RACE	MEN WITH CORONARY DISEASE						ENTIRE ARMY (PER CENT)
	FATAL CASES		SURVIVORS		TOTAL		
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
White	421	93.5	363	90.7	784	92.2	90.0*
Negro	26	5.8	37	9.3	63	7.4	10.0
Filipino	1				1		
Mexican	1	0.7			1	0.4	
Chinese	1				1		
Total	450	100.0	400	100.0	850	100.0	100.0

*Includes all races other than Negro.

Comparative comment will be made later concerning the clinical and pathologic features of the disease in the Negroes of this group.

Education: The educational level attained by this group is identical with that for all inductees, an average of 9.6 years of completed schooling.

Marital Status: The percentage of married men in this group is consistent with the percentage for all inductees, which was about 25 per cent.

Previous Occupation: The occupations prior to induction of 233 men who died suddenly of coronary artery disease and of the 400 men who survived an attack of acute myocardial infarction, together with a comparison of the distribution of these occupations among all inductees, are shown in Table III. There appears to be a tendency for men with coronary artery disease to have

TABLE III. OCCUPATIONS OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE AS COMPARED WITH ALL INDUCTEES

OCCUPATION	MEN WITH CORONARY DISEASE			ALL INDUCTEES (PER CENT)
	FATAL CASES (PER CENT)	SURVIVORS (PER CENT)	TOTAL (PER CENT)	
Factory and labor	42.7	39.8	41.1	59.4
Clerical and sales	21.6	15.2	17.6	13.3
Service except domestic and protective	15.4	25.8	22.1	10.9
Professional and supervisory	9.3	10.8	10.5	4.5
Farm	5.7	5.8	5.8	6.8
Domestic service	2.2	0.5	1.0	4.0
Protective service	1.8	1.5	1.7	0.9
Students	1.3	0.6	0.2	0.2
Total	100.0	100.0	100.0	100.0
Total cases	233	400	633	

been engaged in the less physically arduous occupations, such as clerical, service, professional, and supervisory, as compared with factory, labor, and farm occupations. Thirty-three per cent of the men with heart disease were engaged in service, professional, and supervisory occupations, as compared with 15 per cent of all inductees engaged in such occupations. There seemed to be an unusually large number of men engaged in occupations concerned with the distribution and use of gasoline. This was an impression and is not apparent in the table.

Master, Dack, and Jaffe[98] discussed occupation in relation to coronary artery thrombosis. Of their 555 patients, 49 per cent were laborers, skilled or unskilled, and 51 per cent ran the gamut of other occupations. The authors concluded that occupation was not a factor. From a study of our series, no definite statement can be made, but the figures are at variance with those of these authors.

Height-Weight Factor: French and Dock,[15] in reporting eighty cases which are also included in the group of fatal cases of this series, concluded that overweight was an important etiological factor in these young men. Although our first impression was similar, when we compared the weights of the men in the "coronary" series with a group of 297 men of the same age group who died as the result of accidents, we found that there was no significant difference. Furthermore, a comparison of the weights at induction of 233 of the men who died as the result of coronary artery disease with those of all inductees of the same age group failed to bring out any significant difference. The men, on the whole, gained weight during their Army careers; and, although it is true that most of those who died of coronary artery disease were overweight in comparison with all inductees, they were no heavier than others who had been in Army service for a time but who did not have coronary artery disease (Table IV and Chart 2).

TABLE IV. DISTRIBUTION OF HEIGHT AND WEIGHT IN FATAL CASES OF CORONARY DISEASE AS COMPARED WITH ALL INDUCTEES AND 297 MEN OF SAME AGE GROUP DEAD OF ACCIDENTS*

HEIGHT-WEIGHT GROUP	AT INDUCTION		AT TIME OF DEATH	
	CORONARY DISEASE PATIENTS (PER CENT)	ALL INDUCTEES (PER CENT)	CORONARY DISEASE PATIENTS (PER CENT)	DEATHS FROM ACCIDENTS (PER CENT)
Markedly underweight	14.2	12.5	4.8	3.5
Underweight	19.7	25.0	9.8	10.5
Normal weight	22.7	25.0	21.0	23.0
Overweight	28.8	25.0	43.4	42.6
Markedly overweight	14.6	12.5	21.0	20.4
Total	100.0	100.0	100.0	100.0
Number of cases	233			

*All data based on men 18 to 39 years of age, inclusive.

TABLE V. HEIGHT AND WEIGHT OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE COMPARED WITH ALL INDUCTEES

WEIGHT-HEIGHT GROUP*	MEN WITH CORONARY DISEASE			ALL INDUCTEES (PER CENT)
	FATAL CASES (PER CENT)	SURVIVORS (PER CENT)	TOTAL (PER CENT)	
Markedly underweight	14.2	11.3	12.7	12.5
Underweight	19.7	20.7	20.5	25.0
Normal weight	22.7	17.8	20.1	25.0
Overweight	28.8	27.0	27.6	25.0
Markedly overweight	14.6	23.2	19.1	12.5
Total	100.0	100.0	100.0	100.0

*Classification of weight in relation to height based on measurements at induction.

In making these comparisons of heights and weights as of the time of death, it must be admitted that the data determined at autopsy are inexact. However, for purposes of this study, in which the weights of the control group were obtained in the same manner, there is no reason to presume that one set of data is biased as compared with the other. The more important figures were those obtained at the time of induction, which were accurately determined.

The heights and weights at the time of induction of the 416 men who survived an attack of acute myocardial infarction are compared in Table V with the same data from 233 of the fatal cases and of all inductees. It is noted that

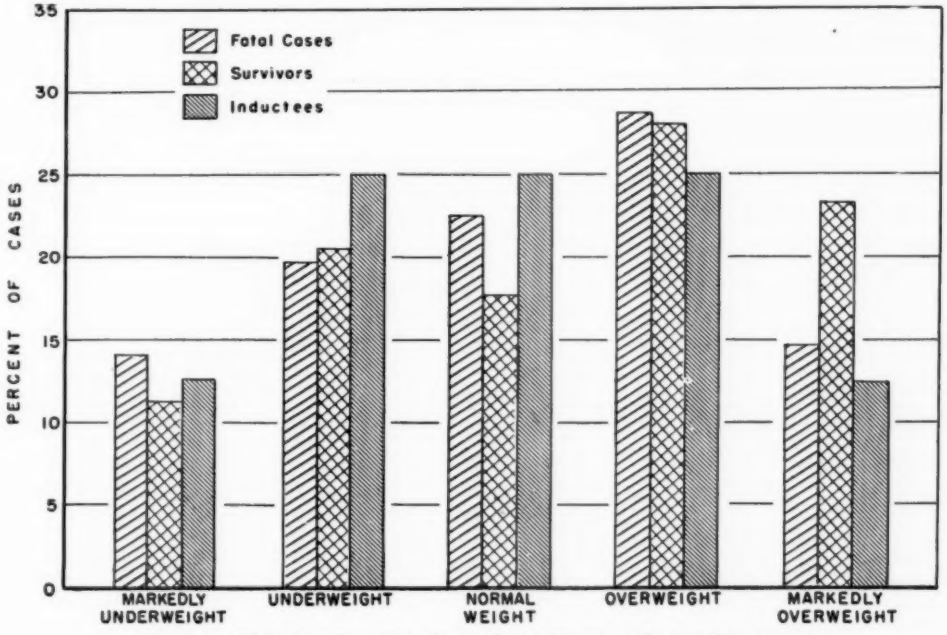

Chart 2.—Height and weight of men 18 to 39 years of age with coronary disease compared with all inductees.

the proportion of markedly overweight men was about 60 per cent greater among the survivors than in the fatal group and about 86 per cent greater among the survivors than for all inductees. The table shows that there is a slight tendency for men with coronary artery disease to be overweight at the time of induction, particularly the survivors of the acute attack, with the deceased patients appearing to be more representative of the Army as a whole.

The standard of reference used for the men at the time of induction was compiled by the Surgeon General's Office from height and weight data collected on 101,142 men at induction stations in January and May of 1943. The definition of obesity is of necessity an arbitrary one. For the purpose of this study, the following height-weight classes were established.

1. The lowest 12.5 per cent of the standard weight distribution for a given height and weight is defined to contain those men markedly underweight.
2. The next 25 per cent is defined to contain those who are underweight.
3. The middle 25 per cent of the standard distribution is defined to contain men who are of normal weight.
4. The next 25 per cent of the standard distribution is defined to contain men who are overweight.
5. The top 12.5 per cent of the standard distribution is defined to contain men who are markedly overweight.

Blood Pressure: The relation between coronary artery disease and blood pressure has been discussed in the literature on heart disease many times. For example, it has been stated that "high blood pressure is more frequently associated with beginning cardiovascular disease than any other discernible sign."[99] It is, therefore, of interest to study this younger group for hypertensive tendencies at the time of induction in order to determine whether there are any indications of prognostic value in blood pressures which might have foreshadowed their death or an attack of myocardial infarction.

Induction blood pressure values were available for 205 patients who died unexpectedly and for 337 patients who survived an attack of acute myocardial infarction. The determinations of the induction blood pressures were made hurriedly and under abnormal conditions. To obtain controlled comparisons, it was desirable to have a group of men whose pressures were taken under the same or similar conditions, and who have, as yet, demonstrated no overt evidence of cardiac disease. As a control group, 210 amputees and other wounded patients, whose records were available through the Veterans Administration, were chosen.

A classification based on the height of blood pressure in millimeters of mercury was arbitrarily established for the analysis:

Normal	110/70 to 139/89	Slightly elevated	140/90 to 159/104
Low normal	100/60 to 109/69	Moderately elevated	160/105 to 199/119
Low	70/50 to 99/59	High	200/120 to 224/129
Very low—under	70/50	Very high	225/130 and above

By classification on this basis of the 205 patients who died suddenly of coronary artery disease and whose induction blood pressures were known and of the control group, the distribution of induction pressures shown in Table VI was

obtained. A slight though definite tendency toward hypertension is evidenced by the patients with coronary artery disease, with 20 per cent of them having had induction pressures above normal as against 5 per cent of the control group. Conversely, 4 per cent of the group with coronary artery disease had pressures below normal as compared with 14 per cent of the control group.

TABLE VI. INDUCTION BLOOD PRESSURES OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH FATAL CORONARY DISEASE AND OF ARMY CONTROL GROUP

BLOOD PRESSURE CLASSIFICATION	MEN WITH FATAL CORONARY DISEASE		ARMY CONTROL GROUP	
	NUMBER	PER CENT	NUMBER	PER CENT
Low			1	13.6
Low normal	8	3.9	28 (29)	
Normal	156	76.1	173	81.2
Slightly elevated	39	19.0	11	5.2
Moderately elevated	2	1.0		
Total	205	100.0	213	100.0

The systolic and diastolic components of the induction pressures of the fatal cases and the survivors were analyzed separately. In addition to the control group of amputees, the patients with coronary artery disease were compared with a large series presented by Alvarez and Stanley,[100] based upon 1,067 white prisoners between the ages of 25 and 29, and another by Robinson and Brucer,[101] based upon 4,039 men between the ages of 20 and 39 years. The Alvarez-Stanley series gave results which were so similar to the Robinson-Brucer series that, for purposes of simplification, only the former series will be utilized in the following discussion.

The Alvarez-Stanley series contained proportionately more patients with lower systolic pressures than either the amputee group or those of this series. However, patients with coronary artery disease showed significantly greater tendencies toward hypertension than either of the other two groups. As shown in Table VII, only 16 per cent of patients with coronary artery disease had systolic pressures under 120 mm. Hg as compared with 42 per cent for the amputee group and 60 per cent for the Alvarez-Stanley series. Similarly, 28 per cent of the group with coronary artery disease had systolic readings above 139 mm. as against 9 per cent for the amputees and 5 per cent for the Alvarez-Stanley series.

The relative incidence of the systolic pressures may be calculated as follows from Table VII, if one assumes that the amputee blood pressure readings are representative of the Army as a whole.

SYSTOLIC PRESSURE (MM. HG)	CORONARY PATIENTS (PER CENT)	ARMY CONTROL (PER CENT)	RELATIVE INCIDENCE (RATIO)
100 to 119	16.4	41.8	0.39
120 to 139	55.7	49.3	1.13
140 to 169	27.9	8.9	3.13

Thus, it will be seen that of the men with coronary disease there were only 39 per cent as many with systolic pressures under 120 mm. Hg as are normally found in the Army, and over three times as many with pressures above 140 mm. of mercury. The relative incidence of coronary disease is more than twice as great in patients with pressures of 140 to 169 mm. Hg as in those with pressures of 100 to 139 mm. of mercury.

TABLE VII. SYSTOLIC BLOOD PRESSURES OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE AND OF ARMY CONTROL GROUP AND ALVAREZ-STANLEY SERIES

INTERVAL (MM. HG)	PER CENT DISTRIBUTION				
	MEN WITH CORONARY DISEASE*			ARMY CONTROL GROUP†	ALVAREZ-STANLEY SERIES
	FATAL CASES	SURVIVORS	TOTAL		
80-89	——	——	——	——	0.6
90-99	——	——	——	——	5.6
100-109	5.9	3.0	4.5	12.7	22.7
110-119	10.7	13.1	11.9	29.1	31.0
120-129	32.8	23.7	28.2	30.5	23.5
130-139	27.8	27.3	27.5	18.8	11.2
140-149	19.0	25.5	22.2	8.9	3.8
150-159	2.9	6.2	4.6	——	1.2
160-169	0.9	1.2	1.1	——	0.4
Total	100.0	100.0	100.0	100.0	100.0
Number of cases	205	337	542	213	4,507

*Pressure taken at induction into Army.

†Composed of amputee patients of the Veterans Administration who showed no signs of cardiovascular involvement.

Essentially the same trend is apparent when the diastolic blood pressures of the patients with coronary disease are compared with those of the control groups. However, it is important to note, in view of the fact that the diastolic pressure is the more significant with regard to the hypertensive trend, that the differences between the groups are somewhat more. Thus, in Table VIII the group with coronary artery disease had 19 per cent with diastolic pressures above 89 mm. Hg compared with 4 per cent for the amputee patients and 5 per cent for the Alvarez-Stanley series.

An analysis of relative incidence for the diastolic pressures similar to that for the systolic pressures yields the following results:

DIASTOLIC PRESSURE (MM. HG)	CORONARY PATIENTS (PER CENT)	ARMY CONTROL (PER CENT)	RELATIVE INCIDENCE (RATIO)
40 to 69	4.8	19.2	0.25
70 to 89	76.1	77.0	0.99
90 to 129	19.1	3.8	5.03

TABLE VIII. DIASTOLIC BLOOD PRESSURES OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE AND OF ARMY CONTROL GROUP AND ALVAREZ-STANLEY SERIES

INTERVAL (MM. HG)	PER CENT DISTRIBUTION				
	MEN WITH CORONARY DISEASE*			ARMY CONTROL GROUP†	ALVAREZ-STANLEY SERIES
	FATAL CASES	SURVIVORS	TOTAL		
40-49	——	——	——	——	2.4
50-59	——	0.3	0.1	1.4	11.8
60-69	5.9	3.6	4.7	17.8	27.1
70-79	36.6	19.8	28.3	44.6	38.7
80-89	46.2	49.3	47.8	32.4	14.7
90-99	9.8	24.6	17.2	3.8	5.0
100-109	1.5	1.8	1.6	——	0.3
110-119	——	0.3	0.2	——	——
120-129	——	0.3	0.1	——	——
Total	100.0	100.0	100.0	100.0	100.0
Number cases	205	337	542	213	4,507

*Pressures were taken at induction into the Army.

†Composed of amputee patients of the Veterans Administration who show no signs of cardiovascular involvement.

Thus, among the patients with coronary artery disease there was but 25 per cent of the normal proportion of men with diastolic pressures under 70 mm. Hg and nearly four times as many as are expected to have diastolic pressures over 89 mm. of mercury. There were, consequently, more than four times as many "coronary deaths" in those having diastolic pressures over 89 mm. Hg at induction as there were among those with diastolic pressures under 90 mm. Hg, relative to the number of persons in each group.

Since at the time of induction 28 per cent of the patients with coronary artery disease had systolic pressures between 140 and 170 mm. Hg and 19 per cent of them had diastolic pressures between 90 and 110 mm. Hg, there is a definite, though moderate, trend toward hypertension in this series. The actual number of patients with definite hypertension, however, is small. It must be pointed out that there is an unknown number of men in this age group who were barred from military service because of hypertension, some of whom may now have coronary artery disease and may later die because of it before they reach the age which limits this series. Therefore, the role of hypertension in relation to coronary artery disease in this age group cannot be accurately determined.

The differences in the per cent distributions of blood pressure, either systolic or diastolic, between the patients who died suddenly of coronary artery disease and those who survived an attack of acute myocardial infarction are much less marked than the differences between the patients and either control series. However, it is of interest to note that the pressures of the surviving patients are higher than those of the patients who died. This may be indicative of a greater ability of members of the former group to adjust to their circulatory needs.

The relationship of hypertension to coronary artery sclerosis and acute coronary artery occlusion has been discussed frequently in the literature. Levine and Brown[102] found that 40 per cent of 145 patients were definitely known to have pressures of 160/100 or more before their attack of coronary thrombosis, but many patients who had a normal blood pressure after the attack showed evidence of pre-existing hypertension in the ocular fundi. Sixty-eight and three-tenths per cent of their patients were between 50 and 69 years of age, and only three were under 40 years of age. Hypertension was present in 33.9 per cent of Connor's[103] 274 cases, with the highest incidence in the age group of 56 to 60 years. Allen[104] reviewed several articles on the relation of hypertension to angina pectoris and coronary occlusion and found that the percentages of cases with occlusion in which hypertension occurred varied from 26 to 59. Of the author's 140 patients with occlusion, 73 per cent had hypertension. Palmer[105] found an incidence of 73 per cent hypertension among 212 cases; hypertension was found in only 37 per cent of patients under 50 years of age at the time of the attack and in 78 to 84 per cent in the sixth, seventh, and eighth decades of life. The average blood pressure before the attack was 170/100. In the follow-up it was found that hypertension developed in more than one-half of the cases within one year after the attack; the incidence increased year by year and finally reached 72 per cent. The pressure failed to return to previous levels in one-half of the nonhypertensive cases and in one-third of the hypertensive cases; in one-third of the hypertensive cases the blood pressure remained permanently normal. Master, Dack, and Jaffe[69] found that 62.4 per cent of 500 patients with myocardial infarction had blood pressures of 150/90 or more and that the frequency of hypertension rose directly with age; for instance, only 28 per cent of the men 25 to 34 years of age had hypertension, whereas it was present in 80 per cent of those 75 years of age or older. Gross and Engelberg[106] found the incidence of hypertension in 100 cases of coronary thrombosis to be 90 per cent. The subsequent blood pressure in hypertensive cases following coronary occlusion had no effect on longevity or on the occurrence or the severity and duration of heart failure. However, Bland and White[107] in a series of 200 cases found that during the first few years following the attack, the hypertension of more than 150/100, which existed in 31 per cent of the patients, had no particular effect, but that the added burden of hypertension greatly increased the mortality over a ten-year period (from 2.6 per cent to 13.2 per cent). Rathe[108] found hypertension in 63 per cent of 274 patients prior to the first attack, and a family history of hypertension, cerebrovascular accident, or cardiovascular disease in 48 per cent of the cases. Of the 202 cases of Master, Dack, and Jaffe[109] hypertension was present in 60.4 per cent before the attack but in only 37 per cent after the attack. The hypertension did not influence the frequency of subsequent attacks of occlusion, but did increase the incidence of heart failure, as in the series of Bland and White. Master, Jaffe, Dack, and Silver[110] found previous hypertension in 69 per cent of 538 patients with coronary occlusion; hypertension was more frequent with multiple than with initial attacks of occlusion. Again they emphasized the increase in the incidence of hypertension with age. In one-third of the cases the blood pressure persisted at a low level throughout the hospital stay, whether

the patient had had hypertension previously or not; in one-third there was a gradual return to the initial levels but not to the high levels preceding the attack.

Chambers[111] found the incidence of hypertension in 100 cases of coronary occlusion with myocardial infarction to be 74 per cent. Of thirty-four patients who died of the acute episode, 71 per cent had hypertension. Over one-half of the patients with hypertension gave a history of angina, dyspnea, or decompensation. Chambers concluded that there was no relation between antecedent hypertension and the mortality rate, but that in the group of hypertensive patients the mortality depended directly upon the degree of hypertension. All of the articles quoted included both male and female patients.

Thus, it appears that there is some relationship between coronary artery disease and hypertension which increases with age. It may be that there is an hereditary predisposition to the two diseases or that there is a common etiological factor. Another possibility is that reduction in the coronary blood flow resulting from disease of the coronary arteries may cause hypertension as a compensatory mechanism to increase the head of pressure in the coronary arterial tree.

PRECIPITATING FACTORS

It is probable, of course, that the coronary artery disease in our patients existed at the time of induction. However, the many possible causes for precipitation of the coronary insufficiency or the thrombosis which brought about the terminal event were investigated.

Type of Service.—It was thought that the type of Army service might have had some influence. The Arms or Services regarded as involving normal activity were listed as Medical Corps, Signal Corps, Finance Department, Military Intelligence, and Adjutant General's Office. Those considered to involve heavy or strenuous activity were Infantry, Air Corps, Ordinance, Artillery, Quartermaster Corps, Armored Forces, and Engineers. It was realized, however, that the Arm or Service in which a man was employed did not permit a very accurate estimate of his duties. Table IX gives an analysis by Arm or Service of 295 of the men who died suddenly. There is no significant evidence to the effect that the Arm or Service affected the rate of death from coronary disease. The proportion of cases within each Arm was about equal to the strength of that Arm, with the single exception of the Artillery in which the incidence of coronary artery disease was 3.4 times the percentage strength of the Arm.

An analysis was also made of the number of men by five-year age groups in the two divisions of Arms or Services. There is no indication that age bears any relation to Arm or Service in determining the occurrence of death from coronary artery disease.

Length of Service.—Table X gives the percentages relating to length of service for 709 men classified according to death or survival from the acute attack. Forty per cent of the men died within one year of entering service. Although there are no accurate data available on length of service for the entire Army, it is probable that the preponderance of men in the Army, perhaps as

TABLE IX. DISTRIBUTION BY ARM OR SERVICE OF 295 FATAL CASES OF CORONARY DISEASE IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE

ARM OF SERVICE	DEATHS FROM CORONARY DISEASE		ENTIRE ARMY (PER CENT)
	NUMBER	PER CENT	
Normal Activity Branches	88	29.8	26.3
Medical Department	23	7.8	5.7
Signal Corps	15	5.1	9.0
Others*	50	16.9	11.6
Heavy Activity Branches	207	70.2	73.7
Infantry	46	15.6	22.7
Air Corps	50	17.0	21.5
Ordinance	11	3.7	7.0
Artillery	38	12.9	3.8
Quartermaster	25	8.5	10.0
Armored Forces	13	4.4	2.5
Engineers	24	8.1	6.2
Total	295	100.0	100.0

*"Others" includes Arms or Services such as Finance Department, Military Intelligence, Adjutant General's Office, and so forth.

much as 98 per cent, had more than one year of service. There is every indication, therefore, that those who suffered an acute attack of coronary insufficiency or myocardial infarction tended to have much less service than the men in the Army as a whole, and that the rigors of military service may have been a factor in precipitating death. Also, in general, if the acute attack was fatal, it occurred earlier in the military career than infarction followed by survival. Thus, 45 per cent of deaths from the acute attack occurred during the first year of service, as compared with 34 per cent of the attacks of acute myocardial infarction which the patients survived.

TABLE X. LENGTH OF ARMY SERVICE PRIOR TO ACUTE ATTACK AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

LENGTH OF SERVICE UNTIL ACUTE ATTACK (MONTHS)	FATAL CASES		SURVIVORS		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
0-6	80	25.9	63	15.7	143	20.1
7-12	60	19.4	73	18.3	133	18.8
13-35	113	36.6	214	53.5	327	46.1
36-71	26	8.4	46	11.5	72	10.2
72-120	4	1.3	1	0.2	5	0.7
Over 120	26	8.4	3	0.8	29	4.1
Unknown	141				141	
Total	450	100.0	400	100.0	850	100.0

The relationship of age to length of service of 279 of the men who died suddenly and the 400 men who survived an attack of acute myocardial infarction was investigated (Table XI). There appeared to be a definite tendency for the older men to die earlier in their Army careers. Only 24 per cent of the men in the 18 to 24-year age group died during the first year, in comparison with 48 per cent of the 25 to 29 year age group, 49 per cent of the 30 to 34-year age group, and 59 per cent of the 35 to 39-year age group. Among the survivors this trend did not exist in the first year of service, but did appear after that time, following the pattern noted in the men who died.

TABLE XI. AGE IN RELATION TO LENGTH OF SERVICE OF MEN 18 TO 39 YEARS OF AGE WITH CORONARY DISEASE; FATAL CASES AND SURVIVORS WITH LESS THAN SIX YEARS OF SERVICE

LENGTH OF SERVICE (MONTHS)	AGE GROUP								TOTAL 18 TO 39 YEARS	
	18 TO 24 YEARS		25 TO 29 YEARS		30 TO 34 YEARS		35 TO 39 YEARS			
	DIED (PER CENT)	SURVIVED (PER CENT)	DIED (PER CENT)	SURVIVED (PER CENT)	DIED (PER CENT)	SURVIVED (PER CENT)	DIED (PER CENT)	SURVIVED (PER CENT)	NUMBER	PER-CENT
0-6	6.9	17.4	28.2	14.8	31.5	15.0	32.1	16.6	146	21.2
7-12	17.2	21.7	19.6	14.8	17.4	18.9	26.8	20.0	137	19.8
13-35	62.1	43.5	43.5	49.1	43.5	53.3	31.3	56.1	333	48.3
36-71	13.8	17.4	8.7	21.3	7.6	12.8	9.8	7.3	74	10.7
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	690	100.0

Time of Year and Place of Death.—When the months of the year in which deaths occurred were analyzed (Table XII), it was found that the probability of death from coronary artery disease or myocardial infarction was fairly evenly distributed by months throughout the year. This was true whether the soldier died suddenly in his acute attack or survived.

Analysis was also made of 235 of the acutely fatal cases as to incidence of deaths in each of four geographic areas: Northeast and North Central, Southeast and South Central, Middle West and Central, and Far West and Northwest (Table XIII). No statistically significant differences existed between the proportion of deaths in the different geographic areas in relation to the number of men stationed in them.

A further analysis was undertaken to determine whether there were seasonal variations in the distribution of deaths within each of the geographical areas. Although the differences were not statistically significant, there was a slight preponderance of deaths during the summer in the Southeast and South Central area. Such data do not take into account, however, the effect of lack of acclimatization, which would be difficult to assay.

These data are at variance with those of most writers on the effect of climate or season (Wolff and White,[1] Wood and Hedley,[112] Mullins,[57] Bean,[63] and Bean

TABLE XII. MONTH OF OCCURRENCE OF ACUTE ATTACK OF CORONARY DISEASE AMONG MEN 18 TO 39 YEARS OF AGE

MONTH	FATAL CASES		SURVIVORS		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
January	27	6.8	40	10.0	67	8.4
February	32	8.0	32	8.0	64	8.0
March	36	9.0	39	9.8	75	9.4
April	27	6.8	38	9.5	65	8.1
May	31	7.8	34	8.5	65	8.1
June	29	7.2	44	11.0	73	9.1
July	33	8.3	34	8.5	67	8.4
August	42	10.5	27	6.8	69	8.6
September	39	9.8	34	8.5	73	9.1
October	41	10.3	29	7.2	70	8.8
November	33	8.3	23	5.7	56	7.0
December	29	7.2	26	6.5	55	7.0
Unknown	51				51	
Total	450	100.0	400	100.0	850	100.0

TABLE XIII. GEOGRAPHIC DISTRIBUTION AT TIME OF DEATH OF MEN 18 TO 39 YEARS OF AGE WITH CORONARY DISEASE

SECTION OF UNITED STATES	DEATHS FROM CORONARY DISEASE		DISTRIBUTION OF ENTIRE ARMY (PER CENT)
	NUMBER	PER CENT	
Northeast and North Central	72	30.6	27.5
Southeast and South Central	93	39.6	46.7
Middle West	48	20.4	18.5
Far West and Northwest	22	9.4	7.3
Total	235	100.0	100.0

and Mills,[113]) who concluded that attacks of acute coronary artery occlusion are definitely more frequent in winter than in summer, especially in north temperate regions. Master, Dack, and Jaffe,[98] noted a higher incidence in December and January for 612 patients, but they did not believe that season was important in determining the incidence of acute attacks.

Activity When Stricken.—There has been considerable contention regarding the effect of activity in inaugurating a "coronary attack," that is, fatal coronary insufficiency (sometimes called fatal angina) or myocardial infarction. Luten,[114] in 1931, expressed the opinion that coronary artery occlusion occurs most commonly during sleep because of lowering of diastolic pressure and lessening of systolic output. On the other hand, Green and Burton,[115] in 1933, concluded from a study of 100 cases that unusual activity or stress or marked departure from ordinary habits of living preceded fatal angina or coronary artery throm-

bosis more often than not, and that many of these departures were preventable. De Santo,[116] in 1935, reported a small group of cases in which operations or violent trauma resulted in arterial occlusion in sclerotic vessels and suggested that occlusion often occurs during or immediately after anesthesia when consciousness is absent or dulled. In 1936, Phipps[117] in a study of 437 cases noted that physical stress appeared to be related to the onset of the attack in 23 per cent, but that in 8 per cent it occurred during sleep, and in the majority of cases, during rest or mild or unusual physical exertion. Bean[63] (1937), in a study based on 300 autopsies selected from 9,626 consecutive protocols, found that in forty-four cases of infarction the onset of symptoms occurred while the patients were at rest, sixteen of them being asleep; in forty-four, during activity; in fourteen, while the patients were eating; and in four, while the patients were deeply intoxicated. In a study of 817 attacks or coronary artery thrombosis occurring in 555 patients, Master, Dack, and Jaffe[98] (1937) found that 21.7 per cent occurred while the patient was at rest, 19.6 per cent while he was asleep, 13.6 per cent during mild activity, 5.3 per cent during moderate activity, and 18 per cent while the patient was walking; thus, 41.3 per cent occurred while the patient was at rest or sleeping and 36.9 per cent during mild or moderate activity. In only 2.1 per cent was there a history of unusual or severe exertion. These authors concluded that there is no one factor or group of factors responsible for the onset of an attack of coronary artery thrombosis and that the apparent association of an attack with some external condition is merely coincidental. In another article[118] the same authors arrived at the same conclusion and added that 4.1 per cent of attacks occurred following surgical operations, a circumstance they considered to be significant. Later, in 1941, Master, Dack, and Jaffe[119] studied the precipitating factors of the premonitory symptoms of coronary artery occlusion in seventy cases and concluded that effort did not initiate them any more than it did those in the case of complete occlusion. However, in 1944, Master,[120] in defining angina pectoris, acute coronary insufficiency, and coronary occlusion, expressed the opinion that acute coronary insufficiency is associated with a precipitating factor which might be either an increased demand for coronary blood flow or anything which actually reduced the flow.

Paterson,[121] in 1939, pointed out that hours or days might elapse between the time of inception of a thrombus in a coronary artery and the moment when occlusion, with its resulting cardiac pain, occurred, and that, therefore, the activity of the patient at the time when symptoms arose did not necessarily solve the problem as to whether activity had any effect in the production of coronary artery occlusion. He considered rupture of intimal capillaries a prime factor in precipitating thrombotic occlusion and was of the opinion that exertion or emotional stress might easily increase the pressure in a capillary of an atheromatous plaque to the point of rupture. Softening of atheromatous tissues surrounding and supporting the capillary walls would still further increase the likelihood of rupture under such conditions.

Boas,[122] in 1939, also stated that trauma to intimal capillaries, either by nonpenetrating thoracic injuries or unusual effort, was in some instances the cause of subintimal hemorrhages which resulted in thrombosis.

Smith, Sauls, and Ballew,[75] in 1942, discussed the events associated with the immediate "attack" in fifty-three of 100 cases of coronary occlusion. In thirty-two, physical exertion was associated with the attack; in ten, bed rest; in five, a heavy meal; in four, a severe emotional upset; and in two, a major operation. In 1941, Blumgart, Schlesinger, and Zoll[123] concluded that shock, no matter how produced, in elderly patients, particularly those showing evidence of arteriosclerosis, may lead to the development, not only of single, but often of multiple fresh coronary arterial occlusions as well. Later (1945), Blumgart[124] attacked the thesis that unusual exertion does not play a precipitating role in certain cases. He pointed out that other factors in addition to effort and emotional stress, such as fatigue, exposure, cold, and eating, place an increased burden of work on the heart. He was interested also in the occurrence of myocardial infarction without coronary artery occlusion, which he thought could be due to relative ischemia. He concluded that subintimal hemorrhage or rupture of an atheromatous abscess could easily be influenced by undue exertion or strain.

Meesen,[84] in 1944, however, was unable to ascribe a causal effect to activity at the time of sudden death of 115 soldiers. He stressed, on the other hand, that there seemed often to be a preceding infection of a respiratory nature.

There was a fairly accurate account of the activity of 324 of the 450 men in the Army series who died and of 363 of the veterans who survived an attack of myocardial infarction. The categories of sleeping, in bed but awake, mild activity, moderate activity, and strenuous activity were established. Mild activity referred to sedentary occupations; moderate activity, to occupations involving ordinary walking; and strenuous activity, to drilling, marching, running, laboring, and participation in sports. Mild and moderate activity, being ordinary or usual, may be grouped together in the final analysis of the effect of activity. Consideration should also be given to the average amount of time spent daily in the various activities. Table XIV gives the numbers and percentages of the two groups of men engaged in the various activities when stricken and the estimated number of hours and percentages spent daily in the different types of

TABLE XIV. ACTIVITY AT ONSET OF ACUTE ATTACK OF MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

ACTIVITY	FATAL CASES		SURVIVORS		TOTAL		ESTIMATED AMOUNT OF TIME SPENT IN EACH ACTIVITY	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER OF HOURS	PER CENT
In bed, sleeping	33	10.2	57	15.7	90	13.1	8	33.3
In bed, awake	38	11.7	18	5.0	56	8.2	0	0.0
Mild-to-moderate	161	49.7	190	52.3	351	51.1	13	54.2
Strenuous	92	28.4	98	27.0	190	27.6	3	12.5
Unknown	126		37		163			
Total	450	100.0	400	100.0	850	100.0	24	100.0

activity. The category "in bed awake" should be discarded in this analysis, since many of the men may have gone to bed because they felt ill.

The analysis shows that the proportion of attacks occurring during strenuous activity was more than twice as great as the proportion of time spent in such activity, that the proportion of attacks occurring during mild or moderate activity was about equal to the proportion of time spent in such activity, but that the proportion of men stricken while asleep was but one-third of what would be expected on the basis of the time normally spent in sleeping. Numerically, the proportion of men engaged in strenuous activity, mild and moderate activity, and sleeping at the time of attack was as 222 to 93 to 39. In the group of fatal cases, more than 75 per cent of the men died rapidly of coronary insufficiency without infarction, whereas in the group of survivors, it may be assumed that most, if not all, had coronary artery occlusion with myocardial infarction; yet the percentages of types of activity for the two groups are strikingly similar.

When an analysis was made of the fatal cases to determine any possible correlation between the type of activity when the soldier was stricken and the type of lesion of the coronary arteries (simple narrowing, practically complete sclerotic occlusion, or thrombotic occlusion) with or without acute myocardial infarction, no correlation was found. However, when an analysis was made of those cases in which there was coronary artery thrombosis in relation to the type of activity when the soldier was stricken, evidence was found to allow the conclusion that there may be a correlation between the age of the obturating thrombus (fresh, organizing, or old) and the type of activity at the time of the attack. Only 11 per cent of those patients with coronary artery thrombosis who died in bed had old or organizing thrombi, whereas 27 per cent of those engaged in mild or moderate activity and 38 per cent of those engaged in strenuous activity had such thrombi (Table XV). Thus, by percentage there were

TABLE XV. AGE OF THROMBUS IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE IN RELATION TO ACTIVITY AT ONSET OF ACUTE ATTACK

AGE OF THROMBUS	ACTIVITY						TOTAL	
	IN BED		MILD OR MODERATE		STRENUOUS			
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Old or organizing	3	11.1	21	27.3	15	37.5	39	27.1
Fresh	24	88.9	56	72.7	25	62.5	105	72.9
Total	27	100.0	77	100.0	40	100.0	144	100.0

three times as many with old or organizing thrombi among those stricken while engaged in strenuous activity as among those found in bed when stricken. From these data it may be concluded that in some cases a thrombus or infarct may have been forming silently for some time and the type of activity at the onset of symptoms was purely coincidental; but that in other cases the type of activity,

particularly if strenuous, may have caused the additional demand for coronary blood flow that precipitated the fatal attack of coronary insufficiency. In the former cases the precipitating factor of the terminal event is unknown but may have been any of several, one of which may have been a generalized vascular relaxation in the presence of a very labile vasomotor system, rather than the much talked of constriction of the coronary arteries.

In the correlation of the presence of fresh thrombi at autopsy with the type of activity, it was found that 89 per cent of thrombi of patients who were in bed were fresh, as compared with 73 per cent of those in patients engaged in mild or moderate activity and 63 per cent of those in patients engaged in strenuous activity. It might be concluded from these figures that rest is more favorable for the formation of thrombi than activity and that death is more likely to occur when the patient with a fresh thrombus is at rest than when he is active; but it cannot be denied that activity may play a part in the production of thrombi. It would appear that although the state of the circulation during sleep is more favorable for thrombosis in a sclerotic artery, it is not as conducive to acute coronary insufficiency as activity when the thrombus is old.

In some cases in which death occurred suddenly, there were features of interest and probable importance in precipitating death. Seventeen men died during or soon after an alcoholic debauch. Seven men, all apparently good swimmers, died while swimming. Five men died during or a few days after a surgical procedure; one, during operation for purulent appendicitis; one, nine days after herniorrhaphy; one, seven days after extraction of teeth; one, two days after incision of a furuncle of the cheek; and one, suddenly after circumcision with local anesthesia. One man died twenty minutes after nicking his finger on a nail; two had had upper respiratory infections a few days before; two were apparently convalescing in hospital from pneumonia; one was convalescing in hospital from chickenpox; one had been treated for sore throat by means of sulfadiazine three days before; and one had had "dysentery" one week before death. One man had been ambulatory for three weeks after an attack of pneumonia when he died suddenly. One man had been struck in the chest by a volley ball two months before death. Another had been struck in the epigastrium with a rock one month before he died.

Analysis of the relationship between the ages of the men and their activity when stricken gave no indication that age was correlated with this factor within the age limits of this series. Neither was there a relationship between the height-weight factor and the type of activity preceding death.

PREVIOUS CARDIAC HISTORY

Of the 450 cases in which necropsy was performed, a previous history was recorded in 242 cases; in 183, death occurred so abruptly that a history was either not obtainable or not reliable, and in twenty-five, a history was either not obtained or not recorded. In these twenty-five cases, the probability is that in most there were no antecedent manifestations of cardiac disease. On the other hand, a careful history was obtainable in all of the 400 cases in which the soldiers sur-

vived. As a result, the history was known and was fairly reliable in 642 of the entire series of 850 cases.

The symptoms preceding the attack were divided into those which were definitely cardiac in origin and those which were of possible or even probable cardiac nature. Table XVI gives the figures relative to the previous cardiac history for the fatal cases and the survivors. In the two groups, the percentages of definite previous cardiac manifestations and of possible ones are almost identical, the percentages for the whole series being 51 with no previous cardiac history, 9 with "premonitory symptoms" which occurred within three weeks of the "attack," thirty-one with a definite history of previous cardiac symptoms for three weeks or more, and nine with a history of possible cardiac symptoms three weeks or more before the attack.

TABLE XVI. PREVIOUS CARDIAC HISTORY OF FATAL AND NON-FATAL CASES IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

PREVIOUS CARDIAC HISTORY	FATAL CASES		SURVIVORS		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
None	123	50.8	202	50.5	325	50.6
"Premonitory" symptoms within three weeks	26	10.7	34	8.5	60	9.3
Definite symptoms (more than three weeks)	65	26.9 49.2	137	34.2 49.5	202	31.5 49.4
Possible symptoms (more than three weeks)	28	11.6	27	6.8	55	8.6
Total	242*	100.0	400	100.0	642	100.0

*The total of 242 is obtained by subtracting 183, the number of men who died so abruptly that the history was either not obtainable or may have been incomplete, and 25, the number of cases in which the history was unknown.

Previous Cardiac Histories of the Fatal (Autopsied) Cases.—Definite or possible cardiac symptoms were said to have been present in 119 of the 242 fatal cases in which a history was obtained. In twenty-six (11 per cent), the symptoms preceded the attack by less than three weeks; therefore, they are arbitrarily designated as premonitory symptoms and as such are considered later in the paper. The symptoms in the other ninety-three cases occurred three weeks or more before the "attack." Of these, in sixty-five (27 per cent) the symptoms were definitely of cardiac origin and in twenty-eight (12 per cent), were possibly or even probably of such origin.

Of the sixty-five cases in which there were definite cardiac symptoms three weeks or more before the "attack," the symptoms were in the nature of anginoid attacks in fifty-seven patients and of partial or complete congestive failure in the other eight. In four patients the anginoid attacks occurred three weeks before death; in one, five weeks; in one, seven weeks; in one, "some weeks"; in six, one month; in three, between one and two months; in eight, between two and three months; in two, five months; in two, six months; in three, between five

and eight months; in one, eight months; in two, ten months; in one, "several months"; in seven, one year; in one, four years; in three, "several years"; in eight, an unstated time; in one, "as long as his friends could remember"; in one, as "repeated attacks"; and in one, "for quite some time."

The pain was substernal in fourteen soldiers; precordial in three; "anginal" in five; precordial, radiating to the left arm in three; precordial, radiating to the arms in one; substernal, radiating to the elbows in one; in the "upper chest," radiating to the shoulders and arms in two; epigastric and substernal with "gas" in one; epigastric and precordial, with palpitation, sweating, and choking in one; precordial with wheezing and dyspnea in one; in the left shoulder and arm followed by precordial pain in one; "in the chest" in one; under the left scapula in one; in the left axilla in one; in the precordium and back in one; and in the left elbow in one. The pain was epigastric with a tight feeling in the arms in one patient. It appeared as tightness in the "chest" and radiated down the arms in one; as discomfort, or vague or evanescent pains, or pains not described in seven; and as "similar to the final pain" in three. Nine men had had anginal pain associated with dyspnea, one with palpitation, choking, and sweating, and one with burning in the throat.

Descriptions of some of the attacks were of interest. One man who had had four attacks of epigastric and precordial pain associated with palpitation, sweating, and choking in the preceding year had been hospitalized twice and on both occasions had returned to full duty. Another man had been hospitalized for two and one-half months because of precordial pain, wheezing, and dyspnea. Another had been hospitalized two weeks before the terminal illness because of chills, chest pain, and cough. Another had had one attack of anginal pain one year before which was diagnosed coronary thrombosis. One man who had had anginal attacks for seven months before death had been hospitalized for one month, six months before with the diagnosis of coronary thrombosis. Another had been hospitalized because of precordial pain with dyspnea one year before and discharged as well; eight months before death he had had a typical attack of myocardial infarction followed by persistent congestive failure. He was found to have an old anterior infarction resulting from thrombotic occlusion of the anterior descending artery. Another man had had pain across the upper chest and arms with nausea, vomiting, diarrhea, and sweating seven weeks before, followed by abdominal pain. This attack was considered a gastrointestinal upset, but although the man had been digitalized because of tachycardia, he had been allowed to be out of bed off and on until he died. One soldier had had an attack of substernal pain radiating to the elbows, lasting five hours, while flying one month before death, followed by another attack the next day, again while he was flying; but there were no more attacks until the night before he died.

As to the frequency of anginoid attacks, six men had had one attack, two had had two attacks, two had had three attacks, three had had four attacks, one had had five attacks, thirteen had had repeated attacks of unstated frequency, and the number was not given for the others.

In a few cases the factors inducing attacks were given; these included exertion, eating, deep breathing, and rest. Some attacks were relieved by rest, belching, vomiting, or deep breathing.

The duration of attacks was rarely given. Three men had had anginal symptoms for four days, one for five days, one for several days, and one for one week. In one patient in whom there had been three bouts of substernal pain at rest and after eating seven weeks before and two bouts after exertion just before hospitalization, the attacks lasted as long as two hours. In another patient in whom there had been one attack of precordial pain one year before the terminal illness, the duration was thirty minutes.

Nine men with anginoid attacks had been hospitalized within seven months of death because of symptoms undoubtedly caused by cardiac disease, although that diagnosis was not made. One had been in the hospital for three weeks one month before death because of attacks of tachycardia followed by dizziness, precordial pain, pain in the left arm and hand, dyspnea, and weakness. The discharge diagnosis was neurocirculatory asthenia. Another had been hospitalized for two weeks two months before death because of tiring on walking; he had epigastric pain, dyspnea on exertion, and excessive perspiration; tachycardia without exertion had been present for two years. He was discharged to duty seven weeks before death, which occurred suddenly while he was drilling. This man was 26 years old, which may account for the medical officer's failure to suspect cardiac disease and request electrocardiographic examination. A third man had been hospitalized two months before death for three weeks because of anginal attacks. An electrocardiogram showed questionable changes, and the diagnosis of neurocirculatory asthenia was made. Another man had been examined at a station hospital three weeks before death because he complained of a dull, heavy, aching pain in the left anterior thoracic region, which had been present since he had been struck there by a medicine ball two months before. Two weeks prior to examination he had also had an attack of epigastric pain and vomiting. Another man was hospitalized for eleven days two months before death because of pain in the chest and dyspnea, both on exertion, of three weeks' duration. The electrocardiogram showed the T wave in Lead IVF to be inverted. On the date of death he reported to the Emergency Room, stating that he had continued to have pain in the chest radiating to the right shoulder after exertion. While leads were being connected for an electrocardiogram he began to gasp for breath and died within a few minutes. Three other cases were similar to this; the patients had been hospitalized for three months, one month, and three weeks, respectively, before death, but a definite diagnosis was not made. The ninth patient had been hospitalized seven months before death for a period of two weeks. Four nights before admission he had awakened with a substernal burning sensation lasting from five to ten minutes; the pain recurred on exertion but was relieved by rest. Examination revealed a small diverticulum of the stomach and a questionable ulcer crater in the duodenum. Electrocardiograms were made on three days. They showed slurred QRS complexes, inverted T wave in Lead IV F, late inversion of T in Lead CF_3, and very slight late inversion of T in Lead CF_5.

Eight of the sixty-five men with definite cardiac symptoms three weeks or more before the "attack" had had symptoms of total congestive failure or of left ventricular weakness. Of the fifty-four men in the autopsy series who were hospitalized during their final illnesses, five had had congestive failure prior to hospitalization. In one man it had been recurrent for seven months before death, and in the others it had existed eight months, four months, three months, and one month, respectively, before the terminal illness. The man who had had congestive failure for eight months had had acute myocardial infarction at the onset of the congestive failure, and the soldier who had had failure for four months had been hospitalized for eight months prior to the onset of failure with a diagnosis of coronary thrombosis. Dyspnea on exertion, other than in the cases of congestive failure already noted, was complained of in three cases; in one patient this symptom had been present one year before and had been associated with a burning sensation in the throat; in one patient it had been present for five months; and in one patient, who had also had nocturnal attacks, it had existed for three weeks.

There were twenty-eight men (12 per cent) who had had symptoms three weeks or more before the "attack" which, in retrospect, were probably of cardiac origin. Ten men had had abdominal pain: one as a dull, aching, epigastric pain one hour after meals for three years; one as attacks of epigastric pain with dyspnea and tachycardia for two years; one with attacks of vomiting for one year; one as vague abdominal pains for "a long time"; one as attacks of epigastric pain, vomiting, and flatulence for seven months; one as left-sided abdominal pain on exertion for five weeks; one as epigastric pain related to meals for one month; and one with "indigestion" after eating. Another man had had epigastric or abdominal pain of such severity two and one-half months before that cholecystectomy had been performed. One man had been told he had an ulcerated stomach one year before.

Three other men had had "indigestion." Another soldier had had diarrhea, vomiting, and fever three months before death and mild abdominal pain with diarrhea for three days before death.

One man had had fainting attacks two years before death; another, spells of weakness and fatigue for one month; another, a spell of weakness one month before death; another, an attack of syncope two months before the terminal illness; and another, "falling out" spells. One man had had attacks of nervousness and sweating for an unstated period, and another, recurrent spells of nervousness and psychic depression during the year before death. One man had had three convulsive seizures in the preceding eleven months. Another had had "asthma" for three weeks eleven years before death.

Two men had had palpitation and tachycardia, one for six months, the other for one month. Another man had had occasional attacks of tachycardia for an indefinite period; he was hospitalized two weeks before the terminal illness with chills, chest pain, and cough.

One man had had slight dyspnea and a tired feeling on exertion for an unstated period. Another had had "cramping pains" in the legs and arms

unrelated to effort for one month; another, pain in the muscles of the legs for two months.

Other facts of interest in the histories of the fatal cases are as follows:

One man had been treated for heart trouble for a year, and another had been hospitalized for nine months for heart trouble and discharged two months before death. One man had been hospitalized for ten days with the diagnosis of chronic nephritis which was not confirmed at autopsy.

In four cases the diagnosis of neurocirculatory asthenia had been made one to two months before death.

Six men had been in a hospital for complaints other than cardiac at the time of death. One of these men had been feeling nervous, irritable, and under tension for three months; four hours before death he became disorientated and was removed to the hospital in a state of alternating dyspnea and convulsions in which he died. Two men* were apparently recovering from pneumonia; one* was convalescing from chickenpox; one* was being operated on for purulent appendicitis; one* had had a herniorrhaphy nine days before death; and one was in the hospital for twenty-four hours with the tentative diagnosis of peptic ulcer.

Only five men were believed to have had previous hypertension, one paroxysmally. In one patient the heart weighed 575 grams, in three it was of normal weight, and in one the weight was not given, the heart presumably being of normal size.

Previous Cardiac Histories of the Men Who Survived.—A definite statement in reference to a past history of cardiovascular disease was available in all 400 cases. Two hundred thirty-six men gave no history of cardiovascular disease before the acute attack. Seventy-three gave a definite history of rather typical angina of effort, sixty-four presented a history of "coronary insufficiency" or other symptoms indicative of pre-existing heart disease, and twenty-seven presented symptoms that indicated possible heart disease, all three weeks or more before the "attack." In addition, there were thirty-four men who had "premonitory" symptoms within three weeks of the "attack." Nineteen men had a knowledge of high blood pressure before the onset of the "acute attack," and six stated that they had had rheumatic fever in childhood but had no symptoms or history suggesting cardiac involvement.

Among the seventy-three soldiers with a typical syndrome of angina of effort, there was a wide range in the length of time that the symptoms were present before the actual "acute coronary attack." One man had had anginal attacks for three weeks, one for four weeks, three for six weeks, three for eight weeks, three for ten weeks, one for four months, three for five months, twelve for six months, six for eight months, two for nine months, fourteen for one year, two for one and one-half years, three for twenty months, three for two years, one for two and one-half years, one for three years, one for five years, eight for "many" years, and four for an unspecified time.

Of the sixty-four patients with a history indicating "coronary insufficiency" preceding the "acute coronary attack" that resulted in discharge from the Army,

*Previously noted.

eleven not only described typical symptoms of a previous "coronary attack" before they entered the Army, but such a diagnosis had been made by their civilian physicians. Four of them had had attacks one to one and one-half years before; five, about two years before; one, three years before; and one, four years before. All of these men had been hospitalized for from four to eight weeks and had been told they had a "heart attack," but none revealed his history at the time of induction.

Thirteen of the fifty-three remaining patients with a history of symptoms indicative of heart disease had experienced an attack similar to but not as severe as the acute episode in the Army. One patient had had two attacks similar to the present "acute attack" ten years earlier at the age of 23 years; these attacks were less severe than the recent one and the patient had not consulted a physician. One soldier had a similar attack three years before; the pain lasted two hours and the patient was kept in bed for two days, but the physician did not determine the cause of the symptoms. Another man had been kept in bed for one week after a similar attack of severe chest pain three years before, when the diagnosis of neurocirculatory asthenia was made. One man reported an attack like the present one five years earlier, but no physician had been consulted. In another patient a similar attack two years before the "coronary attack" in the Army was diagnosed as neuritis of the left chest. Another veteran had experienced excruciating pain in the chest while playing tennis two years earlier. His physician had told him that he had overtaxed his heart and had kept him in bed for five days; ever since this episode the man had been short of breath on exertion. One man had had a similar attack two and one-half years earlier in which the pain in the chest was followed by loss of consciousness for one-half hour; the attending physician had not given the patient a definite diagnosis. One patient reported a similar attack one year before, but he had not consulted a physician. Two men had experienced similar attacks six months before the "acute coronary attack": In one case, the substernal pain lasted one hour, and in the other, the pain was of very short duration, but since then the patient had been short of breath on slight-to-moderate exertion. Neither man had consulted a physician. One soldier had had a severe chest pain nine months before the main attack; the pain, however, lasted only a few minutes and was followed by symptoms attributed to "indigestion." One patient had had substernal pain four months earlier while in the Army but had not reported the incident to the medical officers. One month before the acute episode, another soldier had experienced chest pain similar in nature but of shorter duration than that of the "acute coronary attack"; he also had not reported.

In seventeen other cases of the fifty-three in which the previous history was indicative of cardiac disease, pain was the outstanding symptom. This pain was somewhat different from that described in the preceding paragraph in that it was not similar to the pain of the "acute coronary attack" that occurred in the Army. One patient had had chest pains for twenty years, beginning when he was about 15 years of age, accompanied by shortness of breath; these symptoms were present irregularly but were not definitely associated with exertion. Another soldier had had severe upper abdominal pain ten years before while being

treated for gastric ulcer; at that time his physician told him that the pain was probably due to heart disease. One man had experienced an attack of chest pain diagnosed as being of cardiac origin but not considered indicative of organic heart disease. Three years before the "acute coronary attack," one patient was hospitalized for pain in the upper abdomen; an electrocardiogram had been taken but no definite diagnosis established; the pain had recurred at least every four weeks but was not associated with exertion. One soldier had had precordial pains for two years, with four or five attacks a month, lasting one minute and not related to exertion. Another man had had an attack two years before the acute attack; the pain occurred twice during training and was located in the left axilla. Three men had had attacks of chest pain one year before the "coronary attack." One of these men was referred to a cardiologist for study because of epigastric pains, but the diagnosis of cardiac disease was not made. Another had had a sudden chest pain of short duration; the pain radiated down both arms and was followed by a brief period of unconsciousness. After being kept at rest for five days, the soldier was returned to active Army duty. The third man had experienced a sudden, severe retrosternal pain while moving heavy boxes; the pain lasted three hours and then disappeared without medical treatment. Seven men had had definite attacks of substernal or precordial pain from two to six months before the "real coronary attack." One man had had dull, aching, precordial pain for six months, usually while he was at rest and never associated with exertion. Another soldier was awakened from sleep five months before the "attack" by a sudden severe pain over the left chest; the pain lasted thirty-six hours, and the soldier did not seek medical attention or remain inactive. Three men had had pain three months before the "acute attack." One had had a sudden attack of precordial pain that lasted one hour; another had noted a severe chest pain that lasted only a few minutes but caused him to sit down to rest; and the third man experienced pain between the scapulae of very short duration and not associated with exertion.

Twenty-three of the fifty-three patients experienced symptoms other than pain and their histories were suggestive of cardiac disease before the "acute coronary attack." In twelve of these cases shortness of breath on exertion was the main symptom. One soldier recalled that dyspnea had been present for "years"; another dated the onset of this symptom back ten years. Six men had had shortness of breath on exertion for from one to four years preceding the coronary attack; one had had dyspnea for five months before the attack; and another had had symptoms for three months. Eight of these men had other symptoms referable to the heart before the "acute attack." One had had a severe attack of palpitation ten years earlier; another recalled a few days of "irregular beating" four years before. One man gave a history of severe smothering spells one year before; since then he had had to drop out of drill because of frequent recurrences. Two men had noted a tightness over the chest associated with difficulty in breathing; these symptoms disappeared after a short rest and did not recur. One man had had a choking sensation in his throat one month before the "attack." One soldier had been told three years previously that

because of his heart his life insurance premium would be higher. Another soldier had stated at induction that he thought that he had heart trouble.

There were three other patients who gave a definite past history of heart disease. Two of these men had been told by their private physicians that they had cardiac enlargement; one had experienced an episode of heart failure two years before but did not know the cause.

Nineteen men stated that they had definite knowledge of high blood pressure before the "acute coronary attack." These elevated blood pressures had been discovered on routine physical examinations for various purposes and, in almost all instances, were not responsible for any symptoms as far as the patient knew.

There were twenty-seven cases in which the history of symptoms previous to the "acute coronary attack" was suggestive of possible cardiac disease. In seventeen, dyspnea on exertion was the outstanding symptom. Two men had had dyspnea for two months before the acute "attack," two for six months, three for one year, five for two years, one for three years, one for four years, one for twenty years, and in two cases the duration was not recorded.

In five cases, upper abdominal distress or pain was the outstanding symptom. One soldier had experienced pain in the epigastrium for six years and had been told that it was due to a stomach condition. One man had had epigastric distress after meals for three years; another for five years had had vague abdominal pains, relieved by soda, and dyspnea which made it necessary for him to sleep with several pillows because of shortness of breath. One veteran reported severe attacks of nausea and epigastric pain attributed to gastritis; there was no similarity between these symptoms and those during the "acute coronary attack." One man over a period of months had had frequent epigastric burning, relieved by soda.

Two men had had intermittent pain over the left chest; it was fleeting, did not radiate, and usually occurred at rest. This symptom had been present for two years and five years, respectively. One man had experienced a severe aching pain in the anterior thighs for one week, five weeks before the acute attack. One soldier had had severe "smothering spells" on three occasions during the year preceding the acute attack. One man had noted fainting and dizzy spells on bending or stooping for several years before the "acute coronary attack."

Premonitory, Preliminary, or Prodromal Manifestations.—The subject of premonitory manifestations of acute coronary artery occlusion is a difficult one to discuss, since any anginoid form of attack, except in established cases of angina pectoris, should be considered to be premonitory until proved otherwise. Of the 242 fatal cases in which a history could be obtained, there were twenty-six in which prodromal manifestations occurred within three weeks of the final phase of the "attack"; there were thirty-four similar cases among the 400 survivors. The symptoms, however, were not significantly different in many cases from symptoms that occurred months and even years before the last episode. Among the fatal cases the symptoms occurred within twenty-four hours in seven cases, within thirty-six hours in one case, within two days in three cases,

within three days in one case, within four days in four cases, within six days in one case, within one week in one case, within eleven days in one case, within several days in one case, within two weeks in three cases, and within three weeks in two cases. Among the survivors the symptoms occurred within two days in one case, within three days in one case, within four days in two cases, within five days in three cases, within one week in four cases, within eight days in one case, within nine days in two cases, within ten days in three cases, within eleven days in one case, within two weeks in six cases, within sixteen days in one case, and within three weeks in nine cases.

Examples of these cases are as follows: One man had pain and a sense of constriction in the upper sternal region one day and again four days later, at which time an electrocardiogram was normal; nine days later he had another attack lasting two hours, when he died. Another had diarrhea on one day and a week later had pain in his right shoulder lasting ten minutes; later the same day he had substernal pain and died. Another man had epigastric pain with "indigestion" and tightness in the chest radiating down both arms, relieved by the use of alkalis; four days later he developed pain in his chest and died. Another man had an ache in his chest and epigastrium, shooting to his back intermittently for several days; on the day of his death he had severe epigastric pains, became unconscious for ten minutes, then sat up in bed and fell over dead. Two days before death a soldier developed severe dyspnea on exertion; he was found dead in bed. Another had both nocturnal dyspnea and dyspnea on exertion for three weeks; he was in the hospital for forty-three days thereafter with signs of pulmonary congestion and died without having had pain at any time. One week before his "coronary attack" a veteran had an attack of nausea with severe burning pain extending from the epigastrium to the neck with weakness of the left arm; twenty-four hours before his severe attack of substernal pain he had a similar attack. Another man had a severe constricting type of pain across the anterior part of the chest accompanied by dyspnea, the attack lasting between one and two hours and being relieved by rest; he was hospitalized for one week, all findings being normal, and returned to duty; his "coronary attack" occurred on the sixteenth day following the first attack of pain. Three weeks before his "coronary attack" a soldier had excruciating pain in the anterior part of the chest; hospitalization was advised, but the man refused and the pain ceased after four hours; the next day the pain recurred with slight exertion but did not reappear until twenty days later when he was going through an obstacle course. Another man had precordial pain and epigastric discomfort with radiation to the left shoulder and arm lasting several hours; he remained on duty but was easily fatigued, and ten days later he had his "coronary attack." Another man had a tight feeling in his chest with dyspnea and nausea lasting six hours; his symptoms recurred the next day while he was running, but he was free of symptoms for four days, when he had a typical "attack." Another man, while walking leisurely, suddenly experienced substernal pain with a sense of heaviness and aching in the shoulder and elbows, the symptoms ceasing with rest after ten minutes; twenty such attacks occurred within nine days, when his major attack developed. Another soldier had had typical angina of effort for a year, but fourteen days

before his severe attack he had a severe pain with dyspnea and a choking sensation while at rest, these symptoms lasting two hours; this syndrome was repeated four days later, but he was symptom free until the "real attack" occurred. While working in a kitchen, a soldier had moderate pain across the lower anterior chest region which lasted a few hours and disappeared only to recur each day for three days; he was free of symptoms for four days, when his severe attack occurred while he was resting. Another man was awakened from sleep with a severe, pressing substernal pain which lasted for one hour, after which he went back to sleep; seven days later he had a similar pain with dyspnea, and six days after that, a recurrence while he was playing cards; he was symptom free for a week, when his "coronary attack" occurred. A baker, while kneading dough, felt pain in the left side of his chest which radiated down his left arm and lasted ten minutes; he felt well thereafter and continued to work until he had a classical attack one week later. The other cases were, in general, similar to these.

Correlation of Previous Cardiac History With Various Lesions Found at Necropsy.—There was no significant evidence that the presence or absence of a previous cardiac history in the fatal cases was correlated with the presence or absence of simple narrowing as the sole lesion of the coronary arteries, or with the presence or absence of sclerotic occlusion of the coronary arteries, or with the presence or absence of thrombotic occlusion of the coronary arteries.

Patients with a definite history of cardiac symptoms tended to have myocardial infarcts more frequently than did those without it; the frequency being 39 per cent in the former group as compared with 22 per cent in the latter (Table XVII). Similarly, there was a greater tendency for such patients to have myocardial scars, the percentages being 77 and 62, respectively (Table XVIII), indicating that scars mean more frequent or more severe previous coronary insufficiency.

TABLE XVII. PREVIOUS CARDIAC HISTORY IN RELATION TO MYOCARDIAL INFARCTS AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

MYOCARDIAL INFARCTS	PREVIOUS CARDIAC HISTORY					
	NONE		DEFINITE		POSSIBLE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
None	97	77.6	40	61.5	22	78.6
Gross	22	17.6	23	35.4	4	14.3
Microscopic	6	4.8	2	3.1	2	7.1
Total	125	100.0	65	100.0	28	100.0

A history of previous definite or possible cardiac disease was given in approximately one-sixth of the cases with simple narrowing alone, in one-fourth of the cases with sclerotic occlusion, in one-fourth of the cases with thrombotic

occlusion, in one-fourth of the cases with gross myocardial infarction, and in somewhat less than one-third of those with myocardial scars.

There was no indication that the presence or absence of a previous cardiac history was related to the age of coronary artery thrombosis (recent, organizing, or old) when it was present.

TABLE XVIII. PREVIOUS CARDIAC HISTORY IN RELATION TO MYOCARDIAL SCARRING AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

SCARRING	PREVIOUS CARDIAC HISTORY					
	NONE		DEFINITE		POSSIBLE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
None	48	38.4	16	24.6	13	46.4
Diffuse	46	36.8	30	46.1	12	42.9
Focal	26	20.8	15	23.1	2	7.1
Both	5	4.0	4	6.2	1	3.6
Total	125	100.0	65	100.0	28	100.0

Duration of Terminal Illness of the Fatal Cases and Correlation With Various Lesions.—Of the 450 fatal cases, death occurred within twenty-four hours of the onset of symptoms in 375 (83 per cent), the exact duration being known in 328 and unknown in forty-seven (because the men were found dead or dying). This suddenness of death in such a large percentage indicated the inability of the coronary circulation of these men to compensate for acute obstruction or for other factors that induce acute coronary insufficiency. Table XIX shows the duration of the terminal illness of the 450 cases.

TABLE XIX. DURATION OF TERMINAL ILLNESS IN FATAL CASES OF CORONARY DISEASE AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE

DURATION	NUMBER	PER CENT
Less than twenty-four hours	375	83.3
Instant death, seconds	138	30.7
1-5 minutes, few minutes	67	14.9
6-15 minutes	18	4.0
16 minutes to 1 hour	15	3.3
1-2 hours	30	6.7
3-11 hours	26	5.8
12-23 hours	9	2.0
Several hours	25	5.5
Unknown	47	10.4
Twenty-four hours or more	75	16.7
1-6 days	33	7.4
1-2 weeks	21	4.7
½-1 month	5	1.1
1-3 months	14	3.1
4-7 months	2	0.4
Total	450	100.0

A comparison was made between the cases in which the terminal illness was less than twenty-four hours and those in which it was twenty-four hours or more. Overall, there was no significant tendency for age to be related to the duration of the terminal illness. However, a somewhat larger proportion of the men whose terminal illness lasted twenty-four hours or more were 35 to 39 years of age than those whose terminal illness lasted less than twenty-four hours.

It was found that of the men whose previous histories were known, 61 per cent who had died within twenty-four hours had definite or possible previous manifestations of cardiac disease, as compared with 52 per cent of the men who lived twenty-four hours or more.

A comparative analysis of the lesions gave no significant indication that the duration was correlated with the presence or absence of simple narrowing as the sole lesion of the coronary arteries, since about 80 per cent of the men of both groups died within twenty-four hours; or with the presence or absence of sclerotic or thrombotic occlusion of the coronary arteries.

As was to be expected, more men with thrombotic occlusion and with myocardial infarction lived "longer," that is, had a significantly longer terminal illness, than those having thrombotic occlusion but no infarction.

In only 2 per cent of the patients who died suddenly (within twenty-four hours) and who had a previous cardiac history were there gross myocardial infarcts, as compared with 27 per cent of the patients in whom the terminal illness lasted twenty-four hours or longer and in whom there was also a previous cardiac history.

Gross myocardial infarcts were observed in 13 per cent of the patients who died suddenly and had no previous history, as compared with 36 per cent of the patients in whom the terminal illness was twenty-four hours or more but in whom there was also no previous cardiac history.

The presence or absence of myocardial scars was not correlated with the duration of the terminal illness, but the patients with scarred hearts and a previous cardiac history tended to live longer. Likewise, there was no indication that the age of coronary artery thrombosis (recent, organizing, or old) was correlated with the duration of the terminal illness, whether there was a previous cardiac history or not.

As might be expected, there was a highly significant indication that the presence of a mural thrombus was related to a duration of the terminal illness of twenty-four hours or more, since infarction is the main cause of mural thrombus formation in this series.

(*To be continued*)

THE STRESS AND THE ELECTROCARDIOGRAM IN THE INDUCED HYPOXEMIA TEST FOR CORONARY INSUFFICIENCY

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THE induced hypoxemia test has been established as a procedure which plays a small but useful role in the diagnosis of coronary sclerosis.[1-3] Proper emphasis has been placed upon the potential dangers of the test.[4] However, if the patients to be subjected to the procedure are properly selected and if precautions in administration of the test are observed, the danger entailed is minimal and does not contraindicate use of the test as a diagnostic adjunct. In the 730 tests carried out at the Mayo Clinic for the diagnosis of coronary sclerosis, no fatalities have occurred. It is now believed that in the majority of the patients who have had an alarming reaction, the patient's age or his affliction by complicating illnesses were etiological factors. The factor of danger, however, does limit application of the procedure in many investigations of clinical and electrocardiographic problems of coronary insufficiency, in which otherwise it would be most valuable.

Other undesirable results that might mitigate the usefulness of the test, even as a diagnostic adjunct, have been considered to be (1) its contribution to errors in diagnosis which occur when a negative reaction to the test is used as a basis for the exclusion of coronary disease, or when a reaction is called positive on the basis of minimal electrocardiographic change, or when a positive reaction obscures the diagnosis in the patient whose symptoms are secondary to a disease other than coronary sclerosis, and (2) unnecessary increase in the cost of and time consumed by a cardiac examination. These undesirable consequences, we believe, can be avoided by a proper conception of the purpose of the test and a sound interpretation of the results obtained.

While our efforts have been directed mainly toward an evaluation of the usefulness of the hypoxemia test as a diagnostic adjunct, the following problems which are related to the application and interpretation of the test have frequently recurred in our minds: The possibility of localizing the segmental coronary sclerosis; the influence of ventricular hypertrophy on the electrocardiographic changes which result from hypoxemia; the application of results of the test to prognosis and to the evaluation of drug therapy and of surgical risk; and, finally, the reasons for the frequent dissociation of the electrocardiographic and pain responses. While many of these problems remain unanswered, in others we shall present some theoretical and experimental explanations.

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Among the tests carried out at the clinic, the number performed on patients with thoracic pain which was believed to be an atypical manifestation of coronary insufficiency is slightly greater than the number carried out on patients with puzzling thoracic distress which was believed to be noncardiac in origin. It is of interest that over a period of seven years, the number of tests performed each year has been about the same. About 10 per cent of the subjects have been physicians. The induced hypoxemia is carried out on about 2 per cent of all patients at the clinic on whom a diagnosis of coronary sclerosis is made.

TECHNIQUE

The actual technique of the test is similar to that of our earlier description.[2] The patient lies in a semireclining position and breathes from a tightly fitted mask a mixture of 10 per cent oxygen in nitrogen. There are unidirectional valves in the mask so that no rebreathing occurs. The mask is connected through a long, wide-caliber tube to a demand regulator which furnishes an adequate flow of the gas mixture no matter what the depth of the inspiration. A by-pass valve on the regulator may be opened, if desired, to give a constant flow. In the tubing between the regulator and the mask there is a T tube with an attached 4 liter rubber reservoir bag into which leads a small tube from the tank which contains 100 per cent oxygen. The regulator is equipped with a slight positive pressure arrangement to minimize the slight subatmospheric pressure in the mask during inspiration. The demand valve apparatus has three advantages over the old constant flow arrangement: (1) the mixture of gas is used economically, (2) the noise of the valve gives an additional check on the patient's respiration, and (3) ventilation rates can be measured. The mask should be fitted with care. When this was done, analyses of the gas within the mask revealed no significant leaks except in a few instances. Analyses of the tanks of oxygen-nitrogen mixture that have been supplied to us have disclosed an oxygen content averaging 10.3 per cent. The greatest variations from this figure have been 9.6 and 11.0 per cent. In this past year, the use of a direct writing electrocardiograph in the test has been of great value, in that the test may be terminated if and when diagnostic electrocardiographic changes appear.

INTERPRETATIONS

The criteria outlined by Levy[4] remain the basis for our interpretations. The exact summated measurements of S-T segment deviation are regarded as of lesser significance than the presence or absence of a type of change which, experience has taught, characterizes the hypoxemia response. The precordial lead in the apical area is by far the most diagnostic lead. Two types of change in this lead occur: the common one is the depression of the S-T segment of more than 2.0 mm. and the rarer change is reversal of the T wave. To be clearly significant, it is believed that the latter change should pertain to T waves of at least 0.3 millivolt.

In our previous article, the difficulty of the interpretation of a pain response was emphasized. Once again it may be said that a test in which the result depends upon an interpretation of the subjective responses of the patient fails to afford

evidence of a particularly useful kind. However, if the transition from a gas mixture which contains 10 per cent oxygen to one which contains 100 per cent oxygen is carried out unknown to the patient with pain, the immediate relief of distress usually may be relied upon as an indication of a positive reaction to the test.

EVALUATION OF THE STRESS

The fact that the results of the test are positive in only about 50 per cent of persons on whom the clinical diagnosis of coronary sclerosis has been made need not be surprising, but it stimulates one's curiosity concerning the factors essential to a positive result. In a subsequent part of this discussion, consideration will be given to the alterations in the responses of the myocardial cells to the excitatory process during the period of hypoxia. If these changes develop and if they produce in the electric field of the heart potential alterations which are manifest in the recorded electrocardiograms, then the reaction to the hypoxemia test is positive. A negative result of the test may be related either to failure of significant alterations in the electric field of the heart to be recorded or to failure of such alterations to develop. That appreciable changes in the electric field are commonly unrecognized, because of their failure to manifest themselves in the electrocardiograms which are recorded routinely, seems unlikely. Therefore, the explanation for the majority of the negative reactions to the test must be related to an actual absence of significant alterations in the sequence of potential changes related to the heart beat.

For the absence, during hypoxia, of appreciable alterations in the electric field of the heart affected by coronary sclerosis two explanations may be proposed. These are (1) that an area of injury does develop but is so distributed within the myocardium that for each dipole oriented in one sense there is another oriented in the opposite sense (in such a circumstance the resulting electric forces would cancel each other) and (2) that no area of injury develops. The latter is the simplest and probably the correct explanation for most of the negative reactions to the test. But acceptance of the latter explanation provokes an inquiry into those factors in cardiovascular function which determine whether or not such an area of injury develops in a heart affected by coronary sclerosis. Barach and co-workers[5] elucidated the problem, in part, by demonstrating the great difference in the arterial hemoglobin saturations among patients breathing mixtures low in oxygen and the protective effects of administering carbon dioxide. Further evaluation of the physiologic disturbances in normal persons breathing low concentrations of oxygen have been published very recently by Dripps and Comroe.[6] Their data supply further evidence of the variation in individual response in arterial oxygen saturation, ventilation, and cardiac output under hypoxemic conditions.

There are many factors, some rather intangible, that might contribute to the presence or absence of an area of injury within the myocardium. Among the many variables one has to consider are (1) the degree of increase in cardiac work during the test; (2) the degree of increase in oxygen demand for the same work due to dilatation of the heart (or epinephrine effect); (3) a difference in the amount of oxygen delivered to the myocardium from a unit of blood, which is

dependent upon the degree of desaturation of the arterial hemoglobin, the latter, in turn, being related to an increase or decrease in the pH of the blood as well as to unknown factors that limit the degree of desaturation of capillary blood; (4) the capacity of the blood vessels to permit a compensatory increase in coronary flow, a factor which is related, in turn, to the degree of stenosis and to the length of the stenosed part of the vessel; (5) possible variations in the redistribution of coronary flow and drainage; and (6) the amount of coronary vasoconstriction, which may be a response to acapnia, a part of a general reaction to pain, or a paradoxical reaction of diseased blood vessels. To certain of these factors more extended consideration will now be given.

(1) In order to determine cardiac work one needs values for both cardiac output and blood pressure; without measurements of cardiac output there are no available figures for the expenditure of energy by the heart. In certain patients in whom the test is performed, neither the blood pressure nor the pulse rate increases, although in most patients there is a rise in blood pressure of about 10 mm. of mercury, both systolic and diastolic, and an increase of 20 to 30 beats per minute in pulse rate. In a few patients there may be a more definite pressor response with increases in systolic pressure of 30 to 50 mm. of mercury and increases in diastolic pressure of 15 to 20 mm. of mercury, such reactions being usually associated with moderate tachycardia. A decrease in pulse rate of 10 to 30 beats without change in blood pressure is occasionally observed. Among the few unfavorable reactions, circulatory collapse with rapid fall in blood pressure is the most common. In our cases this condition was complicated on two occasions by cardiac asystole for as long as four seconds.

Except for one instance in which the electrocardiographic abnormality occurred during a marked hypotensive reaction, we have not observed any correlation between the results of the test and the behavior of the blood pressure and pulse rate. One must assume that the combination of hypertension and hypoxemia would increase the stress. Yet it has been particularly noted that those few patients on whom a probable diagnosis of coronary sclerosis was made on clinical grounds and who had a strong pressor response, gave also negative reactions to the test. Furthermore, in a certain number of patients with moderately severe, and in a few with severe hypertension, significant electrocardiographic changes did not develop during the test.

On the basis of the facts available, it appears justifiable to conclude that variations in cardiac work are a factor of minor significance in determining the outcome of the hypoxemia test.

(2) The possibility of an increased oxygen demand for the same work is largely theoretical at present and will not be discussed further at this time.

(3) Some data have been obtained bearing on the significance, in the production of electrocardiographic changes, of variations in the amount of oxygen delivered to the myocardium from each unit of blood. In the consideration of this factor it should be remembered that the cardiac venous blood is normally markedly desaturated, unpublished results obtained in our cardiovascular laboratory from catheterization of the coronary sinus in man having shown saturation values as low as 10 per cent.

As part of our routine test, we have determined the values for arterial hemoglobin saturation by means of an oximeter of the Millikan[7] type; marked variation in these values among persons who underwent the test has been observed (Fig. 1). The saturation drops rapidly, usually to values between 80 and 85, followed by a further gradual decrease. Frequently there may be a plateau appearance from

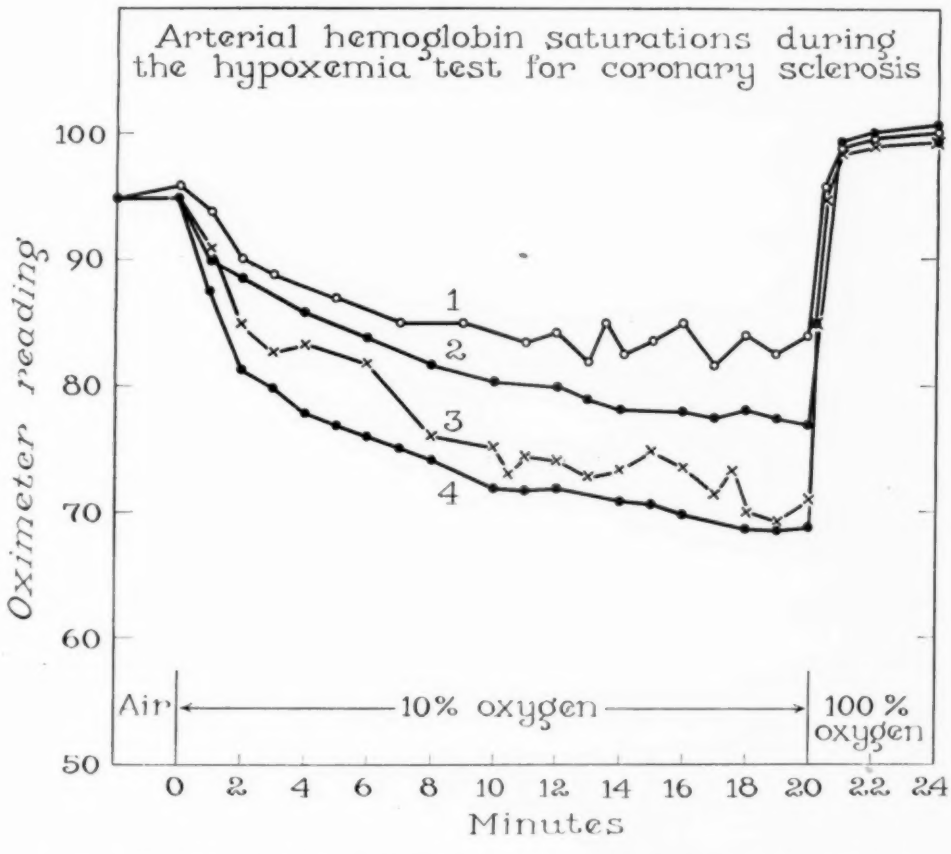

Fig. 1.—Oximeter readings on four patients during a twenty minute period in which 10 per cent oxygen was breathed. Cases were randomly taken to illustrate only the variation in the arterial saturation. The oximeter was arbitrarily adjusted to read 95 when air was being breathed, and in the four subjects shown, the reading became stabilized at 100 when 100 per cent oxygen was being breathed after the test. The ventilation rates and the ventilation per square meter of body surface for the four patients were, respectively: (1) 10.3 and 6.3 liters per minute, (2) 10.0 and 4.6 liters per minute, (3) 6.9 and 4.7 liters per minute, and (4) 8.0 and 4.25 liters per minute. The ventilation was measured for five minutes beginning at the end of the third minute of the test.

about the fourth to the tenth minute, which is followed by a second period of decrease in saturation readings. The values for arterial hemoglobin saturation obtained by this photoelectric method have seemed high but are not incompatible with values calculated from oxygen dissociation curves and alveolar gas equations, if increased pulmonary ventilation is assumed. However, from recent calibrations of our standard oximeters, it is suspected that the oximeter readings in the lower

scale were usually slightly higher than the true values for the arterial saturation. The volumes of expired gas, collected for a period of five minutes in twenty-three patients, and the values for arterial hemoglobin saturation at the end of the period, are shown in Fig. 2. Each sample was collected, beginning three minutes after the

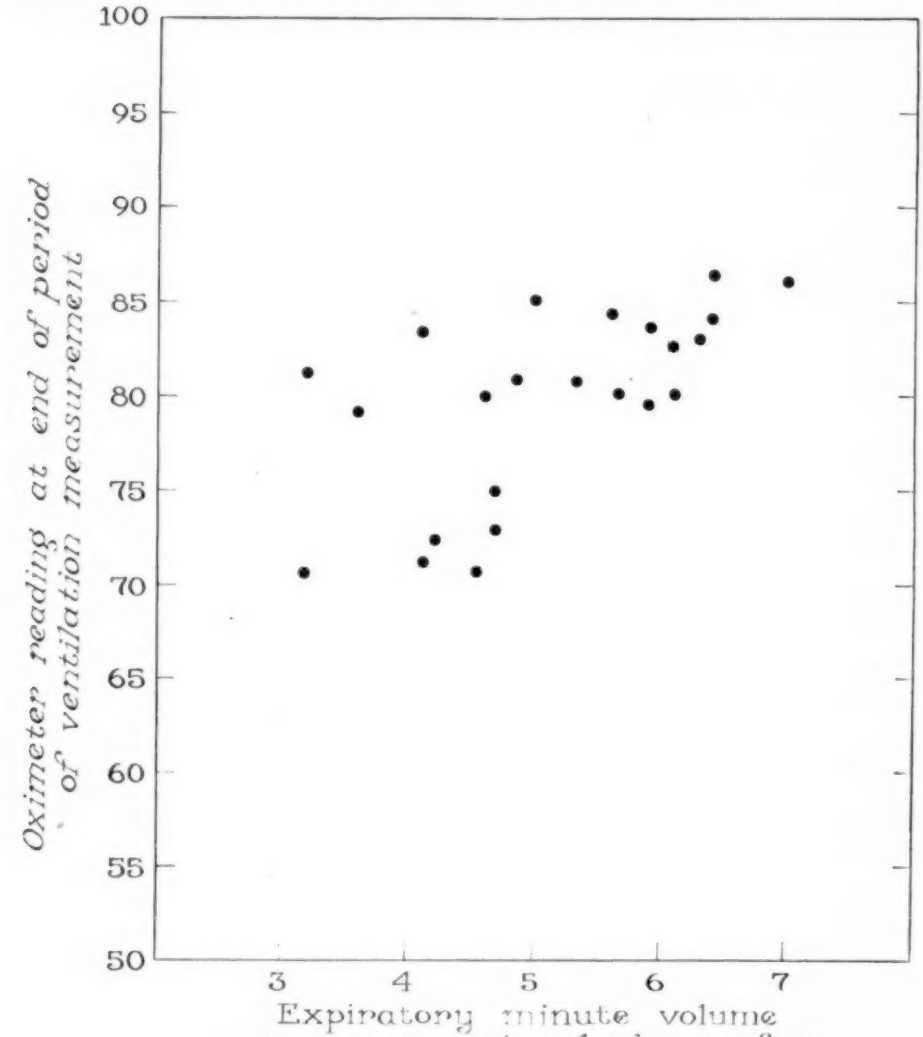

Fig. 2.—The relationship between oximeter readings and ventilation rate in twenty-three patients. The ventilation rate is expressed as the expiratory volume in liters, saturated at room temperature, per square meter of body surface. There is a trend for high oximeter readings to correlate with high expiratory minute volumes. When the actual measured volumes are charted, the scatter is even more marked.

subject had started breathing the oxygen-poor mixture, and was analyzed for content of oxygen and carbon dioxide. The respiratory quotients for pulmonary exchange were almost all greater than one. However, the figures for oxygen

consumption have not been considered entirely reliable. Absorption of nitrogen during this period would produce an error but not of the magnitude encountered. The imperfection in the measurement of oxygen consumption does not invalidate the measurement of ventilation. While there was a general trend for the oximeter reading at the end of the period of the collection of the expired gas (usually the end of the eighth minute of breathing the oxygen-poor mixture) to correlate with the ventilation rate, this relationship is not as direct as might have been expected. The scatter is practically as great when the ventilation is charted as a function of the surface area as when the actual ventilation volumes are charted. So far, we have not been able to obtain sufficiently reliable figures on oxygen consumption in the early period of the test to express the ventilation as a function of the oxygen absorbed.

The degree of desaturation of the arterial blood is not the critical determining factor in the production of a positive reaction to the test (Fig. 3). It is apparent

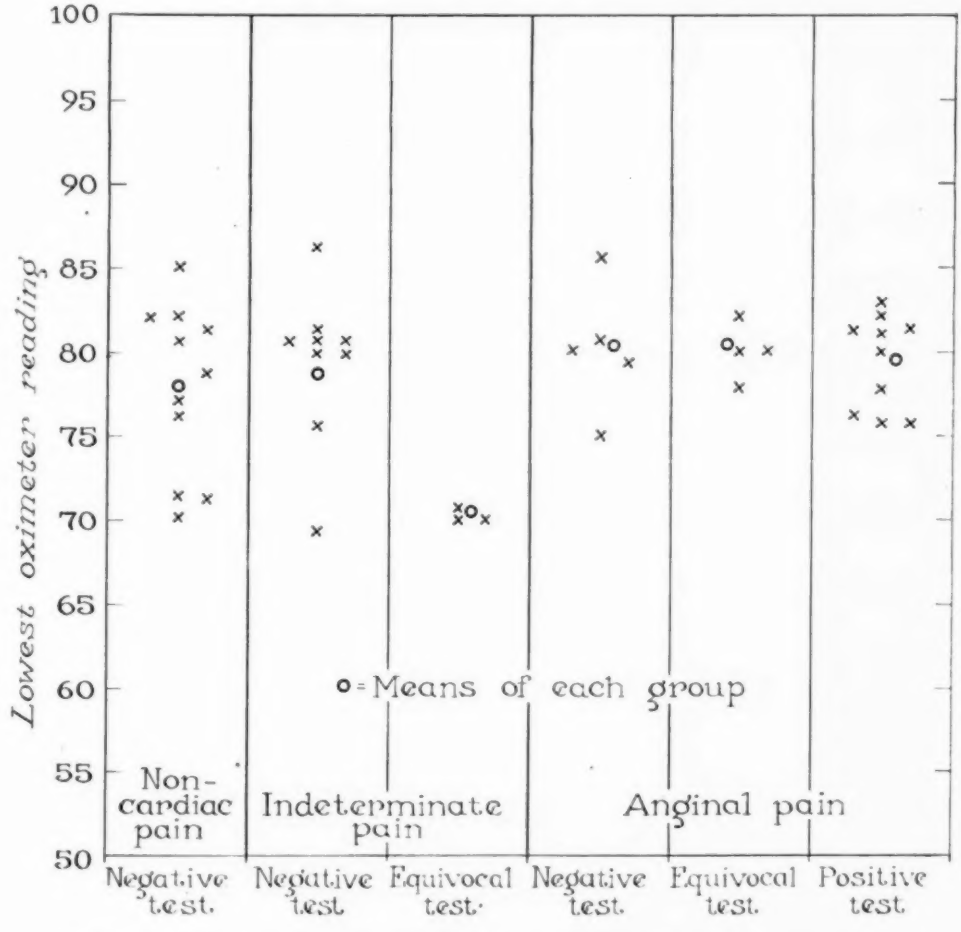

Fig. 3.—The relationship between the lowest oximeter reading during the hypoxemia test and a positive or negative electrocardiographic result.

that those patients having coronary sclerosis clinically and giving a negative reaction to the test had desaturation of a similar degree to that of patients giving positive reactions to the test. In the category of patients labelled as having indeterminate pain, it is believed that a considerable number had coronary sclerosis but the history was so atypical that the making of such a diagnosis was deferred. A few patients with similar atypical pain syndromes were, however, placed in the category of those with anginal pain after a positive reaction to the hypoxemia test was obtained.

(4) The main reason for the development of an area of injury seems to be best related to the inability of the stenotic coronary vessel to allow the tremendous increase of blood flow that normally takes place in anoxia. However, if such were the one and only factor it would be reasonable, perhaps, to assume that electrocardiographic evidence of localized myocardial ischemia would be seen more frequently. Significant evidence related to this problem may be derived from an analysis of the findings at necropsy in the only two cases in our series in which such data are available.

The one man was 43 years of age and gave a history of having had effort distress for ten years. On the first investigation he gave a negative reaction to the induced hypoxemia test. Three months later he experienced sudden thoracic pain while at rest and died in a few minutes. The heart weighed 410 grams, and there was no gross or histologic evidence of acute infarction. Severe atherosclerosis, Grade 3 of the left and Grade 2 of the right coronary artery, was present (graded on the basis of 1 to 4, in which 1 represents the least, and 4 the most severe condition). No acute occlusion was present.

The other patient was a man 50 years of age, who gave a history of having had effort distress for ten years. On the first investigation, he had marked diagnostic segment changes in his electrocardiogram during the hypoxemia test. He returned to the clinic seventeen months later and died suddenly. The heart weighed 530 grams, and there was no gross or histologic evidence of myocardial infarction. The atherosclerosis was graded 2 in the right coronary artery and 3 in both main branches of the left coronary artery. No occlusions were present.

Even from these two cases, which are quite similar in their clinical and pathologic characteristics, it is evident that the severity of the coronary sclerosis is not the sole factor determining whether the outcome of the hypoxemia test is positive or negative.

The evidence seems to indicate that factors of resistance to flow outside the structural limitation contribute to the myocardial ischemia. Among these factors may be those of (5) possible variations in the redistribution of the coronary flow and drainage and (6) the amount of coronary vasoconstriction. Some experimental work[5] has pointed to the importance of a relative acapnia as a contributing factor to the constriction, although the possibility of reflex vasoconstriction cannot be disregarded.

THE "POSITIVE" ELECTROCARDIOGRAM IN THE HYPOXEMIA TEST

As the studies on the hypoxemia test progressed, it was noted that the precordial leads were giving more information than the standard leads and that, indeed, they could be used practically exclusively, if desired. The typical and diagnostic changes in Lead CR_5 were marked depression (more than 2.0 mm.) of the RS-T junction and interval, or a frank reversal of the T wave. In a few instances, the T waves increased in height, a change which is believed to be of possible significance, and in two tests, which are to be discussed in greater detail later, an elevation of the S-T segment occurred.

The commonly occurring depression of the RS-T segment could be explained by a relative positivity of the ventricular cavity during systole. Among the ways this might be accomplished would be through injury of the endocardial layers of the heart, a state attended by incomplete depolarization of the constituent myo-

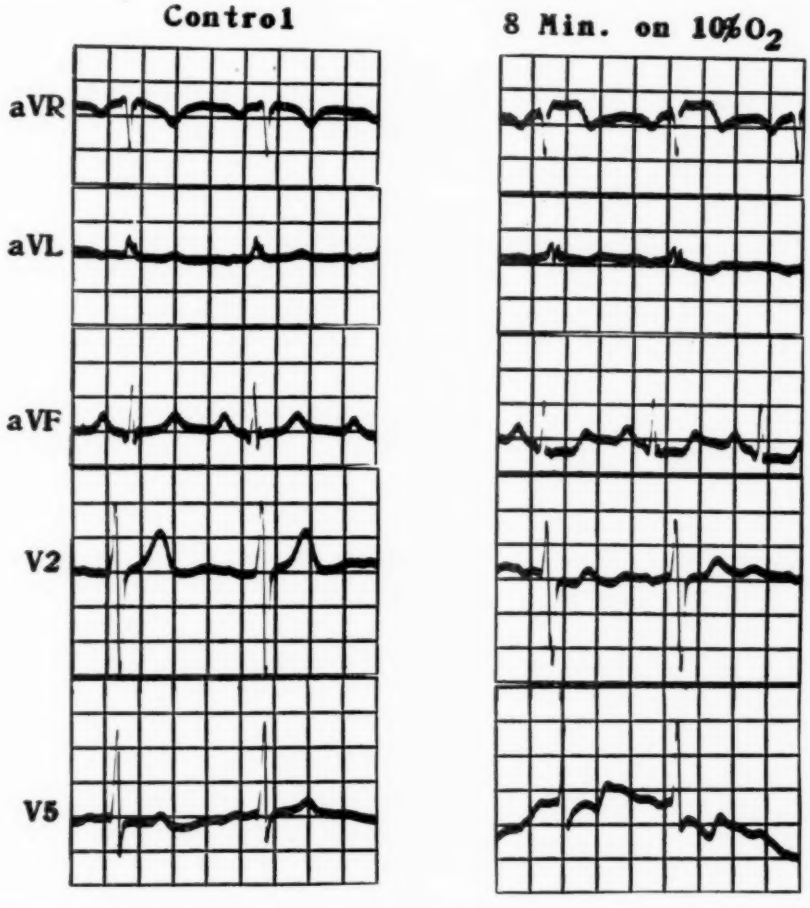

Fig. 4.—Electrocardiographic changes of a positive hypoxemia test with elevation of the S-T segment in the right arm unipolar lead and greatest depression of the S-T segment in the left leg unipolar lead and the apical precordial lead. The heart is in the electrocardiographic vertical position although the electrocardiographic orientation is not a classic type.

cardial cells. No matter what may be the basis of the electrophysical change, it was evident that certain significant data might be added to the information derived from the standard leads and a single precordial lead by measuring the potential differences between right arm, left arm, and left leg, respectively, and a relatively neutral terminal, and by exploring the thorax with multiple precordial leads. In the accompanying sets of electrocardiograms are illustrated certain results obtained by using these additional leads. In Fig. 4, a positive electrocardiographic result is seen with an S-T segment elevation in Lead aV_R

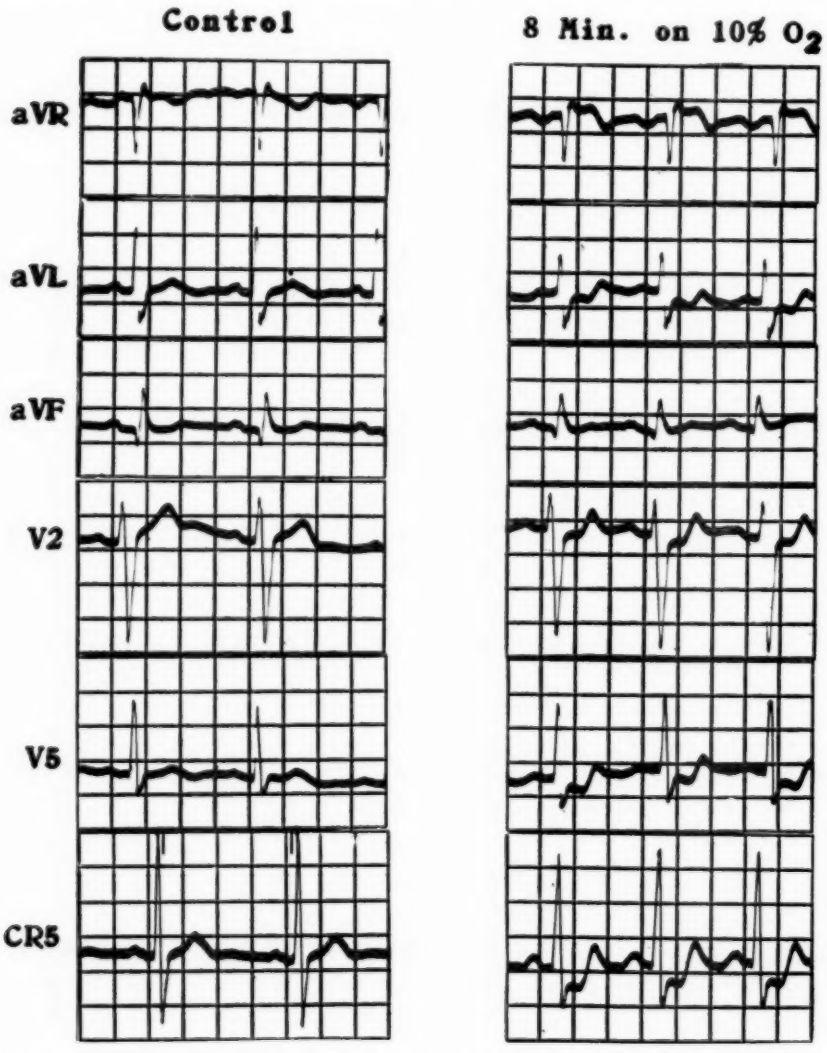

Fig. 5.—Electrocardiographic changes of a positive hypoxemia test with elevation of the S-T segment in the right arm unipolar lead and greatest depression of the S-T segment in the left arm unipolar lead and the apical precordial leads. The greater depression of the S-T segment in the precordial lead when the indifferent electrode was on the right arm instead of the central terminal (Wilson) is well demonstrated.

and S-T segment depressions in Leads aV_F and V_5 in an "electrocardiographically vertical" heart. In other tests, the segment depression was present in aV_L rather than aV_F; this finding occurs in the more "electrocardiographically transverse" heart (Fig. 5). In still other tests, the segment depression may occur about equally in Leads aV_L and aV_F. Evidence has accumulated which indicates that Lead aV_R reflects cavity potential.[8,9] Hence, there is reason to believe that with hypoxemia a potential difference exists across the ventricular wall with an additive manifest potential in the long axis of the left ventricle. An evident explanation for the observation that the segment change is greater in Lead CR_5 than in Lead V_5 exists in the fact that the right arm contributes to, and accentuates, the potential recorded in the former lead. The segment depression observed in the standard leads, usually maximal in Lead II but not infrequently in Lead I, may be similarly explained by the ventricular position.

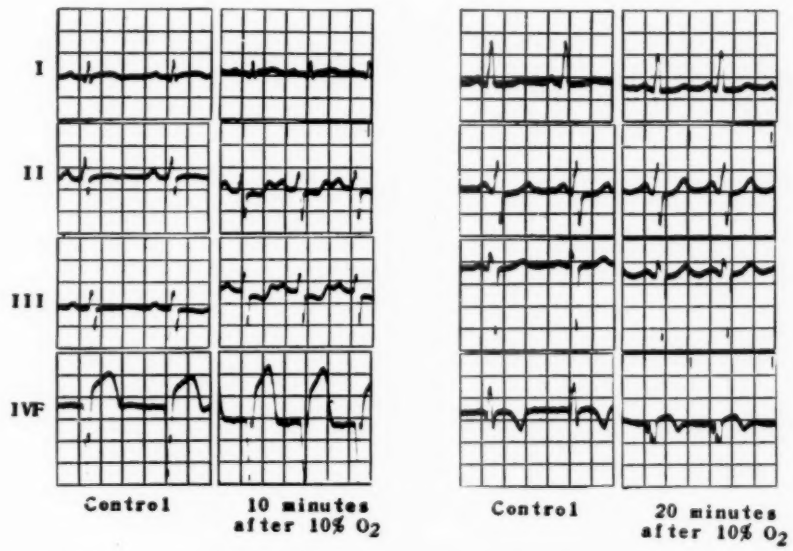

Fig. 6.—The electrocardiographic changes of two patients with hypoxemia who had had a previous anterior myocardial infarction as indicated by the control thoracic leads. The elevation of the S-T segment in the precordial lead is of especial interest and is discussed in the text. The change in the QRS complex of the precordial lead in the tracings on the right may be related to a different orientation of the myocardial scar to the thoracic wall and precordial electrode.

Early in our experience with the procedure, three patients were given the test who had had ancient myocardial infarctions which, before the test was given, had gone unrecognized because of inadequate precordial leads. It is noteworthy that these patients had, in the precordial leads, electrocardiographic changes which were opposite to those of the other patients with electrocardiographically positive reactions to the test. The segment elevation in the precordial lead, with a Q wave and absent R, is a striking effect (Fig. 6). If in explanation of these changes the window theory is utilized, cavity potential is being tapped through the myocardial scar. The results then became compatible with our previous

theoretical discussion. Similar S-T elevations in precordial electrocardiograms in which there was evidence of old anterior apical infarction have been observed by Holzmann[10] in connection with the exercise test.

The reversal of the T wave from a normal positive is rather infrequent and can be explained on the basis of ischemia of the myocardium. Perhaps more interesting theoretically is the reversal of an inverted to an upright T wave. In

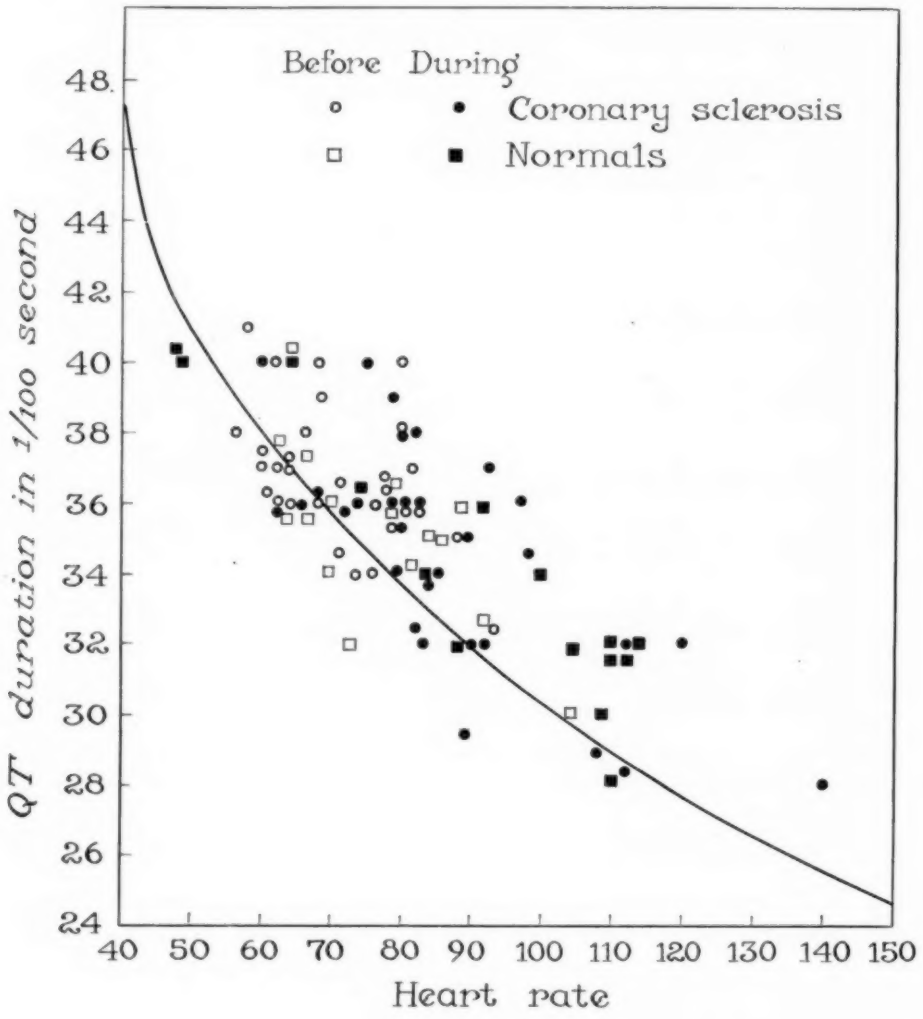

Fig. 7.—The Q-T intervals before and after twenty minutes of hypoxemia in fifteen patients without heart disease ("normals"), fifteen patients with coronary sclerosis and a negative reaction to the test on electrocardiographic examination, and fifteen patients with coronary sclerosis and a positive reaction to the test on electrocardiographic examination. In the majority of instances the Q-T interval shortens or lengthens with the increase or decrease in cardiac rate following a normal relationship. In two patients with coronary sclerosis and a negative reaction to the test, there was an absolute increase in Q-T duration in spite of moderate tachycardia, the significance of which is not known. The change in heart rates may be noted to be slight to moderate. The line representing the mean values for Q-T intervals in relationship to heart rate is taken from Koch's[14] "Allegemeine Elektrokardiographie."

addition to these changes, one occasionally sees increased voltage of the precordial T wave, a reversal of the usual change with hypoxemia; this is believed to be an alteration suggestive of coronary insufficiency.[2]

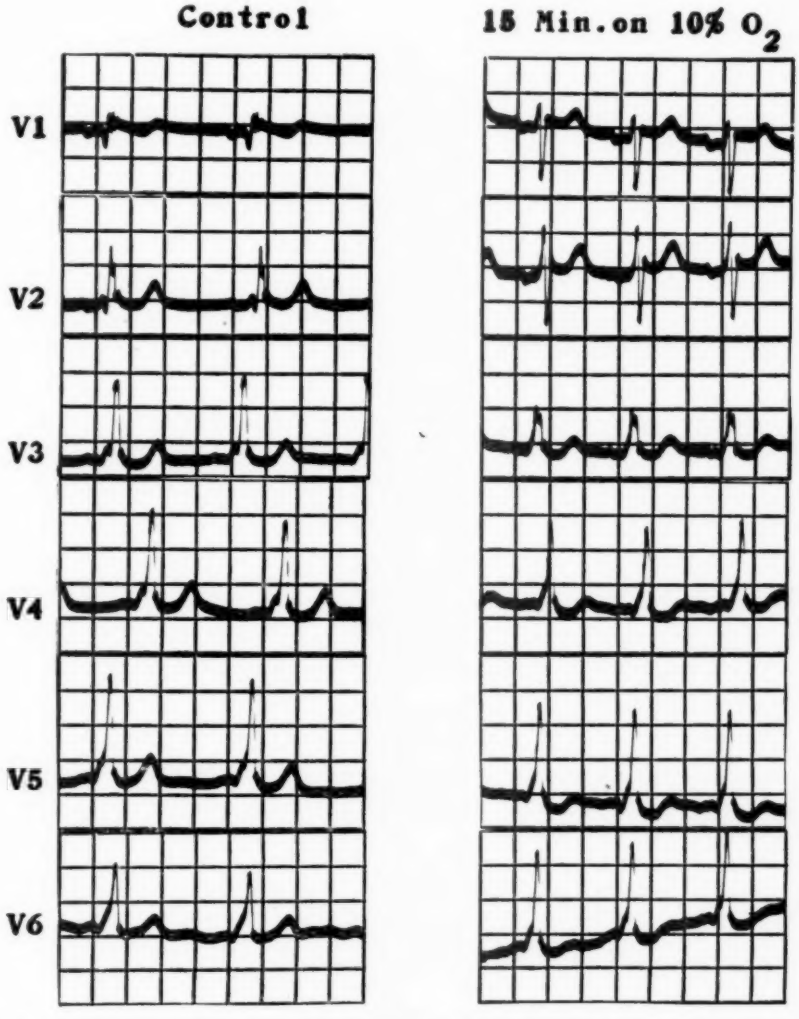

Fig. 8.—Electrocardiograms of the Wolff-Parkinson-White syndrome type in a patient suspected of having coronary insufficiency. Two hypoxemia tests two years apart showed identical changes but the interpretation is difficult. While the electrocardiographic changes observed during the period of hypoxemia are considered to be supportive of the diagnosis of coronary sclerosis, the diagnosis from both clinical and electrocardiographic viewpoints has been deferred.

A change in the duration of the P-R, QRS, or Q-T intervals of degree sufficient to be of value in the interpretation of the test has rarely occurred. In one case, left branch block developed during the period of induced hypoxemia but later an intermittent block was observed to occur frequently without any change in the patient's environment. The Q-T intervals usually follow the normal

relationship to the cycle length but, in rare instances, persons with coronary sclerosis showed an opposite relationship, with the Q-T interval increasing to the upper limit of normal (Fig. 7). This has happened with and without other changes in the electrocardiogram. As there is some evidence[11] to indicate that the systolic index in normal persons under hypoxic conditions first shortens and then greatly lengthens as the subject approaches a state of collapse, further doubt should be entertained as to the dependence of Q-T changes upon the presence of coronary insufficiency during the test.

In an occasional patient, ventricular extrasystoles appeared during the test and, if these were frequent, the procedure was terminated. The significance of the appearance of such an arrhythmia is unknown but it has been assumed that it might create an increased hazard.

When the control electrocardiograms have shown abnormalities of any type, we have been hesitant to interpret further moderate changes which occurred during hypoxemia as evidence of coronary insufficiency. Our experience is quite small in such a group, as patients with ventricular hypertrophy, those taking digitalis and those with definite electrocardiographic deviations from normal, do not require a hypoxemia test for diagnosis. The problem, however, is illustrated by a patient having the Wolff-Parkinson-White syndrome and atypical thoracic pain (Fig. 8). The electrocardiograms made during the hypoxemic stress show changes, but these changes are not beyond the range of abnormality that may exist in this syndrome without such stress.

FOLLOW-UP STUDY ON PATIENTS WHO HAD HAD THE HYPOXEMIA TEST

An attempt was made to obtain information on the patients who had been given the hypoxemia test for coronary insufficiency during the first three years it was used, allowing follow-up periods of three to six years. Questionnaires were sent to 300 patients and reports were obtained concerning 204. Of these 204 patients traced, twelve were not considered further because they had had an unsatisfactory hypoxemia test; thirty were dead and there was presumptive or definite evidence that each death was related to coronary insufficiency (Table I).

TABLE I. DATA ON TWO HUNDRED AND EIGHTY-EIGHT PATIENTS THREE TO SIX YEARS AFTER A SATISFACTORY INDUCED HYPOXEMIA TEST FOR THE DIAGNOSIS OF CORONARY SCLEROSIS

CLINICAL DIAGNOSIS AND RESULT OF HYPOXEMIA TEST	PATIENTS		CONDITION			NOT TRACED
	TOTAL	TRACED	SAME OR IMPROVED	WORSE	PATIENTS DEAD	
Angina pectoris, positive test	86	57	30	11	16	29
Angina pectoris, negative test	45	33	17	10	6	12
Possible anginal syndrome, negative test	56	39	26	6	7	17
Noncardiac thoracic distress, negative test	101	63	57	5	1	38
Total	288	192	130	32	30	96

The average age of the group of thirty patients who died was 47 years, with a range of from 35 to 60 years. The average duration of life after the test in this group was eighteen months, with a range of from three days to forty-four months.

Of this group of thirty patients, nine had normal control tracings and a pain response; of these nine, seven had positive and two had equivocal results in the electrocardiographic study. Of twelve patients with normal control electrocardiograms and marked diagnostic electrocardiographic changes with hypoxemia, seven had pain (Table II). The data might be interpreted as indicating that pain due to true coronary insufficiency is practically always associated with some electrocardiographic changes of the ischemic type but that such electrocardiographic changes frequently occur in hypoxemia without anginal pain.

TABLE II. DATA CONCERNING THIRTY PATIENTS WHO UNDERWENT A SATISFACTORY INDUCED HYPOXEMIA TEST AND LATER DIED OF CORONARY INSUFFICIENCY

CONTROL ECG	TOTAL	RESULT OF TEST				PAIN
		POSITIVE	EQUIV-OCAL	NEGATIVE	UNSATIS-FACTORY	
Normal (including left axis deviation)	20	12	3	4	1	9
Right axis deviation	1	0	0	1	0	1
Right bundle-branch block	1	0	0	1	0	1
Negative or diphasic T_4	4	1	1	2	0	1
Absent R_4, negative T_4	3	1	2	0	0	2
Left axis deviation and digitalis	1	1	0	0	0	0
Total	30	15	6	8	1	14

COMMENT

The experience gained from the performance of approximately 730 induced hypoxemia tests for the diagnosis of coronary sclerosis after the method of Levy has reaffirmed our previous views as to the clinical value of the test. In selected cases the test has been of great assistance in the diagnosis of coronary insufficiency, and when coronary sclerosis of clinical magnitude is present, one may expect a positive result in about 50 per cent of cases. There has been an understandable tendency sometimes to employ the procedure as an exclusion test; one must constantly be on guard to avoid such an error. Among the patients who have been studied are a large number of physicians, young patients with essential hyperlipemia, and patients with diaphragmatic hernias. In the last group of cases, the test has not infrequently supported the clinical impression that symptoms were related to coronary insufficiency and not directly to the hernia. So far, it has been impossible to ascertain the degree of coronary disease that must be present before a positive reaction to the test is obtained, but it is known that severe sclerosis may be present with a negative reaction.

The continuous study of the arterial saturation throughout the test has added to our knowledge of the physiologic stress imposed, but otherwise it has

been of only slight help in the interpretation of the results. Positive results have been obtained both with the low and the fairly high arterial hemoglobin saturations. One gains some knowledge of the ventilatory function during the test so that one can caution the patient against excessive ventilation. When saturation values have fallen to less than 75 per cent, and particularly to 70 per cent, our attention to the patient's condition has been further alerted and such a low saturation has not been allowed to continue for more than a few minutes. For the routine test, the incorporation of the oximeter is not necessary, although the only disadvantage to the use of the oximeter has been the longer control period that is required to permit proper equilibration of the instrument.

One may emphasize again the precautions which must be observed in order that the test may be called a safe clinical procedure. First, in the selection of the patients the following persons should be excluded: those who are more than 60 years old, those with obviously enlarged hearts, those with previous myocardial infarction, those with pulmonary disease, such as emphysema, and those who are generally ill. Secondly, the physician who has some familiarity with the patient's symptoms should personally supervise the test. The knowledge that death from anoxia can occur at relatively low altitudes[12] has not caused decrease in one's respect for the severity of the stress imposed by the hypoxemia test. However, the short time the patient is exposed to low oxygen tensions undoubtedly constitutes an important safety factor.

Our opinion as to the increased stress imposed upon the subject when the test is performed in localities at higher altitudes than that of Rochester has not changed since our first report. The stress is increased, but partial protection is present through the normal acclimatization to altitude. It is believed that the choice of a 10 per cent oxygen mixture was a fortunate one, and at this time we would doubt the wisdom of using a lower percentage.

Our studies with special electrocardiographic leads, namely, the unipolar extremity leads which have been routinely used in the test for eighteen months, have elucidated the genesis of the electrocardiographic pattern but have not contributed significantly to the evaluation of a positive or negative electrocardiographic test. Our electrocardiographic interpretations support the theory that a gradient of injury, increasing toward the endocardium, exists, which is consistent with the theory of injury discussed by Johnston and Wilson.[13] As the interpretation of the test is based on the quantitation of the electrocardiographic changes, it is expedient to use leads where these changes are summated. For this reason the CR leads have certain advantages in the routine tests.

SUMMARY AND CONCLUSIONS

1. The various factors that may contribute to the stress imposed on the heart in coronary sclerosis by the breathing of a mixture of 10 per cent oxygen in nitrogen are discussed. Two cases are cited to indicate that a similar severe degree of coronary sclerosis may be present in patients with a negative or positive reaction to the test. The conclusion is drawn that, in many cases, coronary vasoconstriction is an important factor in determining whether an area of injury develops within the myocardium.

2. In practically all patients, increased ventilation occurs and apparently there is a rough correlation between the extent of increase in ventilation and the degree of arterial hemoglobin saturation.

3. The degree of arterial hemoglobin saturation is not the main factor which determines whether a positive or negative reaction to the test occurs in persons with coronary sclerosis. A physiologically unsteady state is present throughout the whole period of the induced hypoxemia and comparisons cannot be justly made to determinations wherein equilibrium has been established. The brief duration of the test is a safety factor. It is believed that the period of exposure to low oxygen tension may be shortened from twenty minutes to fifteen minutes without significantly reducing the percentage of positive results.

4. Patients with moderate hypertension and cardiac enlargement apparently give a positive reaction to the test only if coronary insufficiency related to coronary sclerosis is also present.

5. The electrocardiographic changes follow a pattern which is consistent with, and supportive of, the concepts of the dipole theory as they are related to a myocardial injury wherein the more seriously affected cells lie in the endocardial layer.

6. The disturbed myocardial state giving rise to the electrocardiographic changes during the test may exist independently of the physiologic stimulus for pain.

7. Patients with coronary sclerosis and a positive reaction to the test have as good a prognosis as those with a negative reaction.

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MYOCARDITIS ASSOCIATED WITH ACUTE AND SUBACUTE GLOMERULONEPHRITIS

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MYOCARDIAL failure has been recognized as a possible concomitant of acute glomerulonephritis for some time. Goodhart[1] (1879) was probably the first to implicate the heart muscle as the cause of cardiac failure in this condition. He reported fatalities in six children in whom nephritis had developed subsequent to scarlet fever; two of the deaths were unexpected. Autopsy examinations were made in five, disclosing a dilated heart in each instance; there were no microscopic studies. Master and co-workers[2] stated that myocardial insufficiency is common in patients with acute glomerulonephritis and may at times be severe enough to cause death; they found it in eight of the twenty-four patients they studied. They related cardiac functional impairment to actual myocardial damage and not to left ventricular exhaustion from suddenly increased peripheral resistance. Impressed by the paucity of significant anatomic changes in the routine heart sections examined (one autopsy from their series and six others), they suggested that the profound changes in the blood and tissue electrolytes altered capillary permeability, which, in turn, caused myocardial damage. Nonetheless, their report includes one instance of serous myocarditis and several of edema of the musculature of the heart. Whitehill and associates[3] found that 71 per cent of their series of 138 patients with acute nephritis showed clinical evidence of cardiac insufficiency; however, these authors expressed the opinion that microscopically the heart muscle was "almost universally reported as being normal, or at the best slightly edematous." They also found that the incidence of myocardial failure encountered varied in direct proportion to the severity of the nephritis. Proger,[4] impressed by the failure to find significant lesions in the myocardium, postulated that the clinical manifestations commonly thought to be indicative of left ventricular failure in myocarditis were in reality evidence of an increase in the pulmonary blood volume produced by some unspecified extracardiac mechanism.

Failure to find appreciable morphologic change in the heart was not universal. Darrow,[5] describing the heart muscle in a fatal case of acute nephritis following scarlet fever, reported that the bundles were spread apart as if by fluid, and noted perivascular accumulations and diffuse subendocardial infiltrations of

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mononuclear cells; he noted also a few plasma cells, but no polymorphonuclear leucocytes. No conclusions as to etiological factors could be drawn because of the antecedent scarlet fever. Three cases of myocarditis with acute nephritis were included in the review by Saphir,[6] but a brief survey of the literature indicates a lack of adequate pathologic data to explain this frequent functional disturbance.

MATERIAL

During a review of the material available at the Army Institute of Pathology a number of cases were found in which myocarditis was associated with acute and subacute glomerulonephritis. Excluding cases of acute nephritis occurring subsequent to illnesses such as scarlet fever, typhus fever, or septicemia (which in themselves may produce significant myocardial changes), this complication was found in sixteen of 160 fatal cases of acute and subacute glomerulonephritis. The information gathered from the records and from examinations of prepared slides from these cases form the substance of this report. All sixteen patients were men. Their ages ranged from 20 to 49 years, but most were between 20 and 30 years of age. All of them presented the characteristic clinical manifestations of acute glomerulonephritis. Often the history of an acute infection of the upper respiratory tract preceded the onset of renal disturbances, and one patient was known to have had an acute antecedent pyogenic infection of the skin.

CLINICAL OBSERVATIONS

The majority of the fatalities in the cases of glomerulonephritis were attributable to heart failure. This condition was recognized clinically in six patients (Cases 2, 4, 8, 9, 10, and 16) but not in six others, although the records included similar clinical observations. In two additional cases the recorded evidence of myocardial failure was limited to the rapid development of pulmonary edema in one and a striking disproportion of pulse and temperature (90 per minute and 104°F) in the other. The two remaining patients died of bronchopneumonia and renal insufficiency, respectively.

There were four unexpected deaths; however, these patients had shown various manifestations of heart failure. The signs and symptoms regarded as indicative of impaired cardiac function were as follows: cyanosis and dyspnea, which occurred in eleven patients; disturbances of rhythm in fourteen (tachycardia in ten, gallop rhythm in three, and auricular fibrillation in one); bradycardia (relative to the temperature) in five; hypotension in three; a weak, thready pulse in two; and ankle edema unassociated with facial edema in two. Electrocardiographic tracings were available for four patients and were abnormal in three. Cheyne-Stokes respiration occurred once. Six of the patients were given sulfonamides and five, penicillin; eight received fluids intravenously. Tables and brief clinical synopses are included to facilitate clinicopathologic correlations (Table I).

TABLE I. CLINICAL MANIFESTATIONS OF MYOCARDITIS ASSOCIATED WITH ACUTE AND SUBACUTE GLOMERULONEPHRITIS

MANIFESTATION	CASES IN WHICH MANIFESTATION OCCURRED
Cyanosis	1, 4, 7, 8, 10, 11, and 13
Dyspnea and/or orthopnea	1, 2, 4, 5, 6, 7, 8, 9, 11, and 13
Cheyne-Stokes respiration	11
Tachycardia	1, 2, 3, 4, 7, 8, 10, 11, 13, and 14
Relative bradycardia	5, 6, 7, 15, and 16
Gallop rhythm	1, 2, and 8
Auricular fibrillation	16
Abnormal electrocardiograms*	2, 4, and 16
Unexpected deaths	2, 3, 4, and 9
Hypotension and/or weak pulse	1, 4, 7, 11, and 15
Precordial pain	7 and 9

*The only other electrocardiogram recorded was normal (Case 15).

PATHOLOGIC OBSERVATIONS

Gross.—At autopsy the viscera of all subjects exhibited passive hyperemia. Marked pulmonary edema had occurred in eight; in thirteen there were accumulations of fluid in the serous spaces. Unrelated pathologic findings included bronchopneumonia in nine, small pulmonary infarcts in the presence of a fractured leg in one, and purpuric manifestations in another.

The kidneys were uniformly enlarged and increased in weight; most of them were red and congested, but pallor was noted in a few. The histologic appearance of all sixteen corresponded to Bell's[7] description of the condition he has designated diffuse proliferative glomerulonephritis. Eleven had the histologic characteristics of acute intracapillary nephritis. In one additional case in which sulfonamides were used, there was a superimposed distal nephron nephrosis. The remaining cases showed sufficient additional changes to warrant classification as subacute nephritis in two and acute to subacute nephritis in two instances.

The hearts were usually increased in weight: three weighed 500 grams; seven, between 400 and 500 grams; two, between 300 and 400 grams; and two were considered of normal weight: 250 grams and 270 grams, respectively. Qualitative alterations described in twelve hearts included dilatation in nine and grossly recognizable changes in the myocardium in eight. Such changes included softening of the myocardium, or pallor, mottling, or streaking of the heart muscle. Table II summarizes these data.

Microscopic.—As in other forms of myocarditis the distribution of the lesions was patchy and not all areas of the musculature were equally involved. There was no evident predilection for or special vulnerability of any part of the heart. The process was mainly of the interstitial type, and evidence of muscle necrosis or destruction was rare and inconspicuous (Figs. 1 through 7). Diffuse infiltrates of inflammatory cells were never observed; on the contrary, the inflammatory foci were small and involved only portions of a section. The serous component of the exudate was particularly conspicuous; the interstitial tissues were loosened by

TABLE II. MYOCARDITIS ASSOCIATED WITH ACUTE AND SUBACUTE GLOMERULONEPHRITIS

CASE	DURATION IN DAYS	ACUTE ANTECEDENT RESPIRATORY INFECTION	CLINICAL EVIDENCE OF HEART DISEASE	BLOOD PRESSURE	BLOOD NITROGEN MG. PER CENT	SULFA MEDICATION	INTRAVENOUS FLUIDS	PULMONARY EDEMA	SEROUS EFFUSIONS	BRONCHOPNEUMONIA	OTHER COMPLICATIONS	HEART WEIGHT IN GRAMS	CARDIAC DILATATION	GROSS ABNORMALITIES OF MYOCARDIUM	TYPE OF NEPHRITIS
1	8	+	+	—	—	0	0	+	+	0	0	270	+	+	Acute
2	10	+	+	144/90	Normal	0	+	0	+	+	0	450	+	+	Acute
3	10	0	+	118/70	N.P.N. 195	0	0	+	+	0	0	500	+	0	Acute
4	12	+	+	132/76	B.U.N. 36	+	+	0	+	⊕	Infected chest wound	500	0	0	Acute†
5	13	0	?	—	—	0	+	+	0	0	0	430	—	—	Subacute
6	14	+	+	200/90	—	0	0	+	0	0	0	454	0	+	Acute
7	16	+	+	90/40	N.P.N. 45-120	+	+	0	+	+	0	411	+	+	Acute
8	17	+	+	136/86	—	+	0	0	+	+	0	425	+	0	Acute
9	18	0	+	158/100	B.U.N. 21	0	0	+	+	0	0	450	+	0	Acute
10	19	—	+	135/80	—	0	0	+	+	0	0	450	+	+	Acute
11	19	+	+	90/64	N.P.N. 214	+	+	0	0	⊕	0	Grossly normal			Acute-subacute
12	20	+	0	170/100	N.P.N. 120	+	+	+	+	+	0	379	0	0	Subacute
13	30	+	+	Elev.	—	+	—	0	+	+	Pulmonary infarcts	500	+	0	Acute
14	38	+*	0	112/72	N.P.N. 35	+	0	0	+	⊕	Purpura	250	0	+	Acute
15	38	0	?	100/54	B.U.N. 60-75	0	+	+	+	0	0	340	+	+	Acute
16	53	+	+	138/80	Normal	0	+	0	+	+	Pericarditis	—	—	+	Acute-subacute

*Also an acute pyogenic skin infection one month previously.
†Additionally there was a distal nephron nephrosis.
⊕Streptococcal bronchopneumonia.

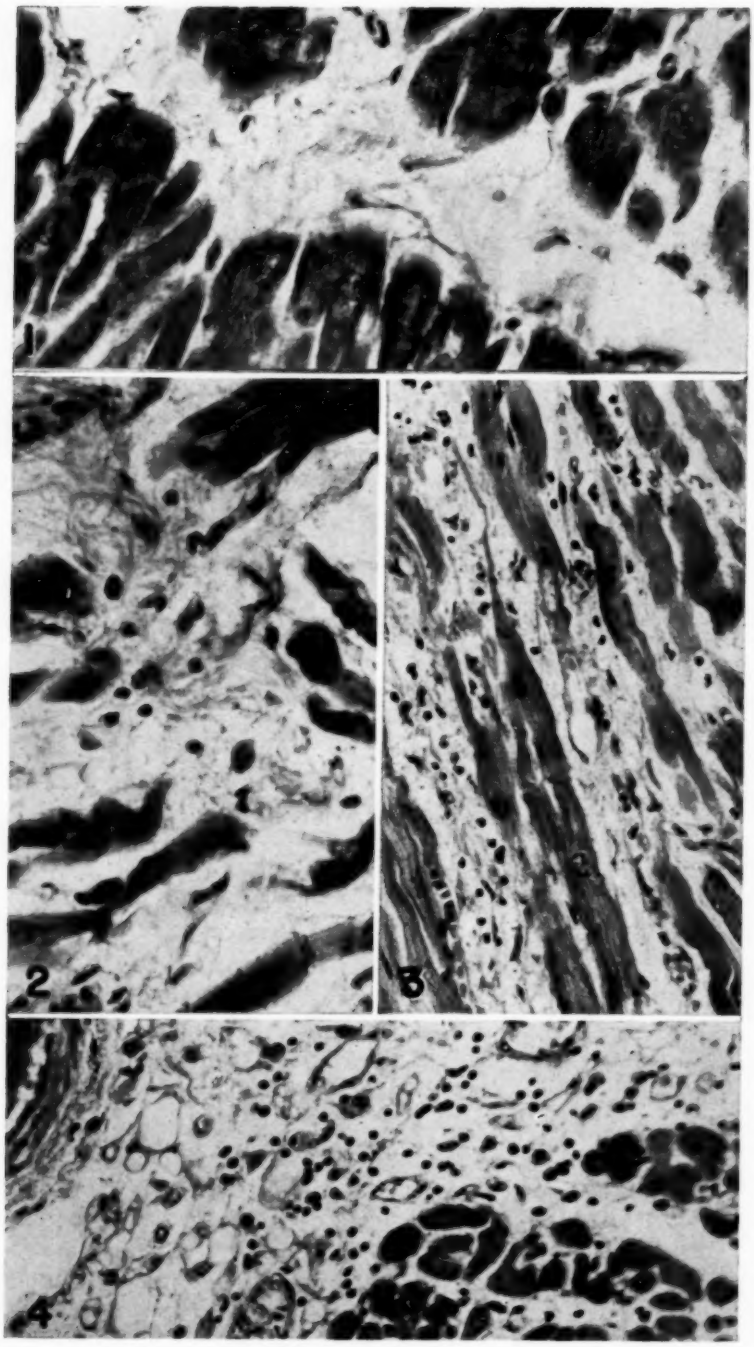

Fig. 1.—(Case 15) Note the serous exudate (edema) within the interstitial tissue. ×435 AIP Neg. 95129.

Fig. 2.—(Case 15) Note the spreading of the muscle fibers by the serous exudate and the very few cellular elements. ×470 AIP Neg. 95119.

Fig. 3.—(Case 15) Note the thinned-out muscle fibers, the serous exudate, and the presence of a predominantly lymphocytic infiltrate. ×315 AIP Neg. 95122.

Fig. 4.—(Case 15) Lymphocytes and a few endothelial leucocytes form the cells of the exudate. ×315 AIP Neg. 95130.

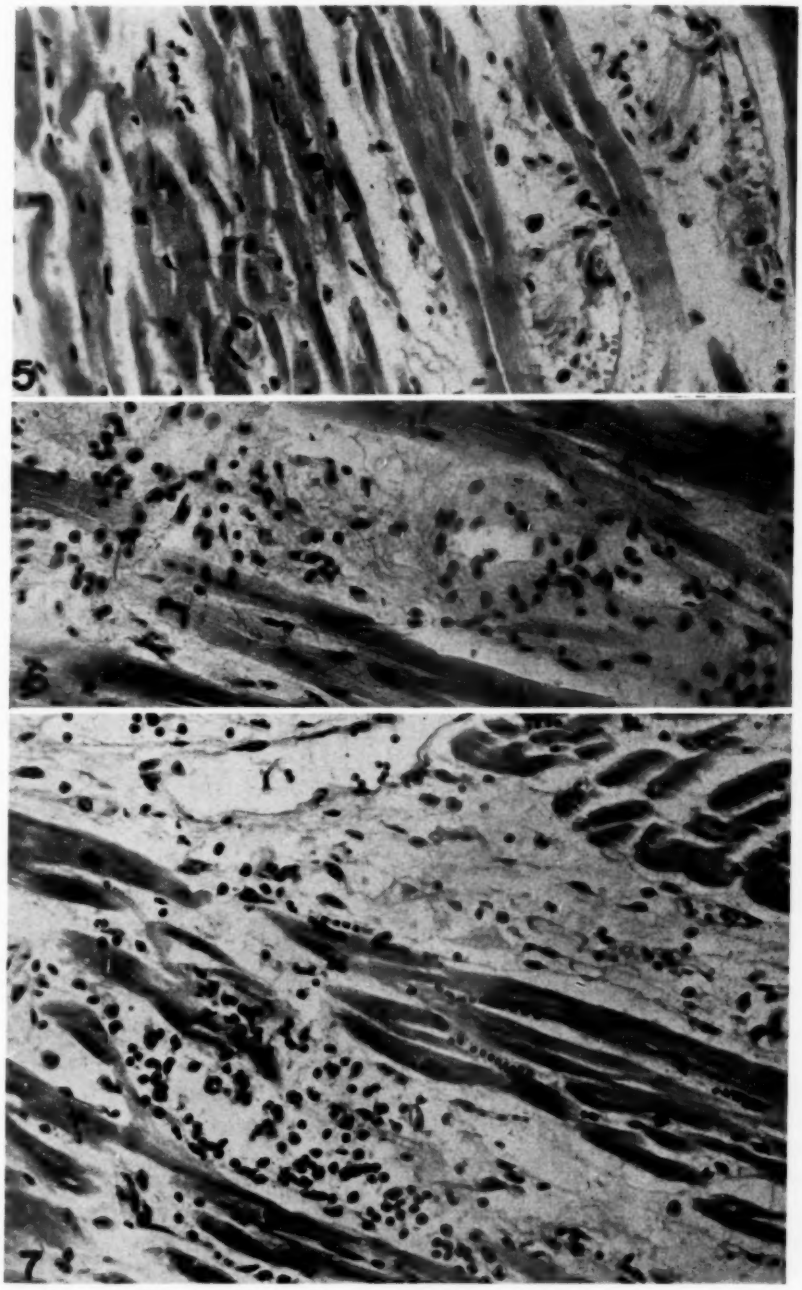

Fig. 5.—(Case 14) A few Aschoff cells and lymphocytes predominate. The muscle fibers are spread by the serous exudate. ×315 AIP Neg. 95110.

Fig. 6.—(Case 9) Many lymphocytes are present, principally in the interstitial spaces, but also tending to displace muscle fibers. ×315 AIP Neg. 95123.

Fig. 7.—(Case 10) Note the many endothelial leucocytes. ×315 AIP Neg. 95112.

the presence of a faintly eosinophilic fluid which dispersed the muscle fibers (Figs. 1 and 2). A small number of inflammatory cells were scattered through the fluid. The proportionate distribution of cells encountered varied from one area to another; lymphocytes and endothelial cells formed the usual and predominant types (Figs. 3 and 4), but Aschoff cells* were often present and, with endothelial cells, sometimes formed the principal cellular elements (Figs. 5 and 6). The occasional eosinophils and mast cells noted did not seem to be an essential part of the exudate. Polymorphonuclear leucocytes were generally absent and there were no structures which could be identified with, or mistaken for Aschoff bodies. The muscle fibers were the seat of varying degrees of cloudy swelling.

DISCUSSION

Considering the high incidence of cardiac insufficiency found clinically in acute glomerulonephritis, we have reported relatively few instances of myocarditis. Our figure, 10 per cent of 160 cases, contrasts sharply with 71 per cent of 138 cases reported by Whitehill and associates,[3] and differs significantly from the 17 to 40 per cent incidence found by various other authors whom they cite. The discrepancy is more apparent than real. Mention has already been made of the patchy distribution of the inflammatory changes in the heart muscle. It is reasonable to assume that in some instances myocarditis was overlooked because the examination of the heart muscle was not sufficiently thorough. The routine sections of myocardium examined in this study constitute but a minute sample of the cardiac musculature.

In consideration of the pathogenesis of the myocardial lesions encountered in these cases of acute nephritis, it is mandatory to evalute the effects of the antecedent infection upon the heart muscle. In another study we have described myocarditis which developed as a result of, or in association with acute infections of the upper respiratory tract. Such illnesses preceded the onset of nephritis in eleven cases of this series. Whitehill and his associates[3] reported that the "onset of nephritis was preceded in about 80 per cent of the [138] patients by more or less severe infections of the tonsils or respiratory tract." As already stated, the type of myocarditis associated with acute glomerulonephritis was characteristically serous, an observation made in those cases both with and without history of recent acute infection. This feature distinguished it from the much more cellular reaction observed in the form of myocarditis associated with acute nasopharyngeal and tonsillar infections. In the latter, too, significant degrees (moderate or marked) of muscle necrosis were common and polymorphonuclear leucocytes were present in appreciable numbers, whereas these were not characteristics of the cardiac lesion associated with acute and subacute glomerulonephritis. Within the time limits covered by these cases, progressive changes in the appearance of the lesions of the heart were not seen, as they so frequently were in the myocarditis associated with acute upper respiratory infections.

*Frequently called the myocyte following Anitschkow's original interpretation, but generally recognized as a type of histiocyte. It plays a conspicuous role in the formation of the Aschoff nodule.

Though the differences between myocarditis of the two forms are clear cut, they do not nullify the role of the antecedent acute infection in the production of the heart lesion. Our knowledge of the lesion is limited to fatal cases in which there may be presumed to be a greater degree or even a different type of involvement than in nonfatal cases. The additional burden created by nephritis and its complications, if this premise is accepted, would be responsible for the fatal termination. Although recent acute infections were not mentioned in the histories of a significant number of these patients, many of the records were made under wartime field conditions and were not nearly as complete as those in other reported studies where the incidence of preliminary acute infections approaches 100 per cent (Whitehill and co-workers,[3] cited previously, reported 97.7 per cent). Two other mechanisms suggest themselves: the first, that the lesion in the heart musculature is the result of the acute nephritis; the second, that cardiac damage is due to the complementary effects of both the acute antecedent infection and the nephritis. The available information at this time does not permit a more definitive statement regarding the causative mechanism.

Nitrogenous retention was absent in only three (Cases 2, 14, and 16) of ten cases in which such blood chemistry studies were made; in an additional instance (Case 9) azotemia was only slight at the time cardiac manifestations had appeared. Such findings suggest, but further data are necessary to prove that uremia neither plays an essential role in the pathogenesis of the cardiac failure nor produces the heart injury by an indirect mechanism, such as the altered capillary permeability resulting from changes in blood and tissue electrolytes. They do tend to indicate the primary role of the heart lesion, although added factors may be the cardiotoxic effects attributed directly and indirectly to alterations of blood and tissue electrolytes in uremia. The morphologic character of the lesion suggests a capillary defect leading to increased extravasation of fluid, but the chronologic relation of such a defect to alterations in blood chemistry requires further study. The recognition of primary diffuse endothelial damage in acute glomerulonephritis is, of course, not a new concept.

The administration of sulfonamides to seven of these patients was not of etiological significance in producing the lesion under discussion. The character of the myocarditis was identical both in those who had received the drug and in those who had not. Furthermore, no case presented the lesions described by French[8] in sulfonamide hypersensitivity, namely, the vascular lesions and the perivascular infiltrates rich in acidophilic histiocytes and eosinophils.

Of fourteen hearts for which the figures were recorded, the weight exceeded 400 grams in ten, seven weighing 450 grams or more. Although hypertension is commonly regarded as the explanation for such enlargement, increased tension was present in only four cases (Cases 2, 6, 9, and 13). The elevation was moderate (200/90) in one, mild (158/100) in another, borderline (144/90) in another, and unstated in the fourth; the corresponding heart weights were 454, 450, 450, and 500 grams, respectively. The recorded blood tensions did not attain hypertensive levels in five other instances of cardiac enlargement (Cases 3, 4, 7, 8, and 10). Measurements of the blood pressure were not available for Case 5, nor were the cardiac weights reported in two additional cases without hypertension (Cases

11 and 16). Furthermore, it is questionable whether the degree of enlargement noted could be produced by an assumed moderate hypertension in the short course of the acute illness. For example, it is dubious whether a presumably normal heart could enlarge to 500 grams in ten days (as in Case 3) through muscular hypertrophy alone. The factor common to all the enlarged hearts, then, and the one not incompatible with the relatively short course of the illness is the serous myocarditis. There can be no doubt that such increases of interstitial fluid as are illustrated in accompanying photomicrographs would appreciably augment the weight of the heart.

These arguments must not be construed to deny the importance of hypertension in contributing to the cardiac enlargement observed. The possibility must be entertained that the relatively normal pressures recorded, though taken early during hospitalization, represented a certain degree of vasomotor collapse already present in acutely ill patients. It is generally accepted, though, that acute glomerulonephritis may occur and run its course without hypertension. Furthermore, cardiac enlargement in other forms of myocarditis without pre-existent hypertension has been attributed to the presence of the inflammatory exudate within the heart muscle.[9]

The therapeutic measures to be adopted are those commonly used in the treatment of other forms of cardiac decompensation. Failure to recognize this development, of which hypotension may be one manifestation, may result in the injudicious administration of fluids intravenously to combat "shock." Needless to say, such treatment may precipitate a fatal outcome.

SUMMARY

One hundred sixty cases of anatomically proved acute and subacute glomerulonephritis, exclusive of those subsequent to scarlet fever, typhus fever, or prolonged septicemia, were reviewed to ascertain the presence and the character of any concomitant myocarditis. Such a myocarditis was found to have occurred in sixteen patients; there were clear-cut clinical manifestations of myocardial failure in twelve, and in two others the clinical records suggested it. The symptoms were those common in other forms of heart disease; namely, cyanosis, arrhythmia, temperature-pulse disproportion, and hypotension. Electrocardiographic tracings were abnormal in three of the four cases in which they were available.

The increased heart weights, which were observed frequently, could be correlated better with the presence of myocarditis than with arterial hypertension, which had been noted in only four patients. The myocarditis had a distinctive character that differentiated it easily from that occurring as a result of sulfonamide hypersensitivity or after acute nasopharyngeal and tonsillar infections. Characteristically there was a widespread serous effusion into the interstitial tissues, increasing the space between the muscle fibers. The cellular elements were relatively sparse, consisting of lymphocytes, endothelial leucocytes, and Aschoff cells. The suggestion that myocardial damage is related to increased capillary permeability appears to coincide with the pathologic evidence. With regard to treatment, caution is recommended in the administration of intravenous fluids.

CLINICAL ABSTRACTS

CASE 1.—AIP Acc. 118909. A 26-year-old white man, who experienced progressive difficulty in breathing following a "cold" one week previously, was admitted to the hospital with cyanosis, dyspnea, "wet lungs," enlarged liver, and edema of the ankles. The heart sounds were poor; there was gallop rhythm. The pulse was rapid and thready. Despite morphine sulfate, aminophylline, and oxygen, there was progressive heart failure, and death occurred after one day.

CASE 2.—AIP Acc. 139746. A 37-year-old white man had noted swelling of the hands, feet, and ankles in the last five days of the course of a persistent upper respiratory infection of several weeks' duration. On admission there were facial edema, cardiac enlargement, and muffled heart sounds; blood pressure was 144/90. The roentgenogram showed pulmonary hilar congestion and a heart at the upper limits of normal size. There was moderate anemia, leucocytes numbered 7,000, and chemical composition of the blood was reported as normal. Although there was temporary improvement, dyspnea, tachycardia (140 per minute), gallop rhythm, and pulmonary edema developed suddenly on the fourth hospital day. Electrocardiograms showed changes compatible with myocardial damage. Treatment with morphine sulfate, aminophylline, digitalis, and oxygen was ineffectual, and death occurred on the following day.

CASE 3.—AIP Acc. 166013. A 40-year-old white man was admitted to the hospital with a two-day history of facial and ankle edema, lumbar pain, mild diarrhea, anorexia, and nausea. Urinalysis indicated acute glomerulonephritis; the blood showed considerable nitrogenous retention; the nonprotein nitrogen measured 162 mg. per cent, and the blood pressure was 118/70. The treatment was not specified. The blood nonprotein nitrogen rose to 195 mg. per cent. Tachycardia and pulmonary edema suddenly developed on the eighth day, and death followed rapidly.

CASE 4.—AIP Acc. 154657. A 25-year-old white man contracted a septic sore throat while hospitalized for a penetrating wound of the chest sustained one month previously. Sulfadiazine therapy was instituted. Three days later severe watery diarrhea and vomiting began suddenly, but were effectively combated with paregoric and belladonna. Although the temperature, which had been high, was now 99.4°F., there were physical signs and roentgenologic evidence of a pneumonic process at the base of one lung. A leucocyte count at this time showed a rise to 18,000 from a previous 7,000. Urinalyses were characteristic of acute glomerulonephritis; hemolytic streptococci were grown from a throat culture. The pneumonic process spread to involve both lungs; the temperature was 99.8°F.; the leucocyte count was 13,000; the blood pressure was 132/76. Except for the signs of the pulmonary process, the patient seemed improved. On the seventh day the temperature was 99°F. and the pharyngitis was less severe, but the pulse became weak and rapid and the respirations were labored. Mental disturbances appeared and the blood urea nitrogen measured 36 mg. per cent. The patient was transfused repeatedly. All of one lung except the apex became affected. Cyanosis appeared and persisted despite administration of oxygen. An electrocardiogram showed a prolonged P-R interval and marked sinus tachycardia. Death occurred quite suddenly on the twelfth day of the acute illness.

CASE 5.—AIP Acc. 146450. A 21-year-old white man was admitted to the hospital acutely ill with cough, anorexia, and vomiting of twelve days' duration. The patient was anemic; the white blood cells numbered 11,300. The urinalysis was typical of acute glomerulonephritis. The temperature was 104°F.; pulse rate, 90; and respirations, 24 per minute. There was marked dependent and pulmonary edema. Blood and plasma were given. Death occurred the day after admission.

CASE 6.—AIP Acc. 100802. A 28-year-old Negro man had a two-week history of pain in the lower back and shortness of breath. When admitted to the hospital he was febrile, with a temperature of 101.4°F., pulse rate of 92 per minute, and blood pressure of 204/90. The diagnoses were acute upper respiratory infection and hypertension. There was, however, mild pitting edema of the ankles and roentgenologic evidence of both central congestion of the lungs and an enlarged heart. Urinalysis indicated acute nephritis. Severe dyspnea developed the afternoon of admission; the temperature was 102.8°F., and the pulse rate was 88 per minute. The temperature rose to 105.2° F., and death occurred sixteen hours after admission.

CASE 7.—AIP Acc. 102628. A 20-year-old white man was admitted to the hospital with fever, sore throat, headache, and chills of two days' duration. The temperature was 100.2° F.; pulse rate, 104; and respirations, 24 per minute; white blood cell count was 24,000; blood pressure, 122/80. Physical examination disclosed marked edema and swelling of the throat with purulent exudate on the tonsils. (Two months previously the patient had been hospitalized for acute tonsillitis). Sulfathiazole was administered and frequent throat irrigations were given. On the fifth day, while the temperature was down and there was considerable improvement of the tonsillar infection; the urine showed the characteristic features of acute nephritis. The subsequent course of the illness was marked by oliguria, low-grade fever ranging from 98° to 100.6°F., and hypotension, the blood pressure measuring 90/40. Treatment consisted, in large part, of the administration of intravenous fluid. The blood nonprotein nitrogen rose from 45 mg. per cent on the sixth day to 120 mg. on the tenth hospital day. Precordial pain appeared on the eleventh day of hospitalization. The following day cyanosis, dyspnea, and weak and rapid pulse were noted. Heart sounds were poor and the patient still complained of precordial pain. Although oxygen was administered, death occurred on the thirteenth day.

CASE 8.—AIP Acc. 128718. A 21-year-old white man was hospitalized because of undue fatigability, cough, exertional dyspnea, and questionable edema of the face and extremities, dating from an acute attack of pharyngitis two weeks previously. Cyanosis, orthopnea, and anxiety were noticeable; the heart sounds were rapid and of poor quality. Signs of bronchopneumonia found on physical examination were confirmed roentgenologically. Urinalysis indicated an acute nephritis. The leucocyte count was 21,500. Despite the administration of sulfadiazine, penicillin, and oxygen, the cyanosis and dyspnea continued. Digitalization was started after a gallop rhythm developed. The patient expired on the third day with a temperature of 101°F., the highest fever attained.

CASE 9.—AIP Acc. 147313. A 31-year-old white man was hospitalized five days after the development of periorbital swelling, sore throat, shortness of breath, and dependent edema. There had been oliguria, and on admission the findings of dyspnea, pulmonary râles, and fullness of the upper abdomen suggested congestive heart failure. The heart sounds were normal; pulse rate, 70 per minute; and blood pressure, 130/78. The urine was typical of acute glomerulonephritis; the blood urea nitrogen was 21 mg. per cent. On the fifth hospital day pitting edema of the legs was noted despite bed rest and the use of digitalis. The blood pressure rose slowly to a maximum of 158/100 on the twelfth day. On the thirteenth hospital day the patient died suddenly after the onset of acute "cardiac pain."

CASE 10.—AIP Acc. 145515. A 38-year-old white man was admitted to the hospital a week after extreme weakness and edema of the face and lower extremities had appeared. He was afebrile, and the blood pressure was 140/80. The urinary findings were characteristic of acute glomerulonephritis. Medication consisted of theophylline daily. The patient remained afebrile; one week after admission, cyanosis, short, shallow respiration, pulmonary edema, ascites, and dependent edema were noted. The heart sounds were rapid and distant and the roentgenogram showed cardiac enlargement and pulmonary congestion. Death occurred on the ninth day despite the administration of aminophylline and digitalis.

CASE 11.—AIP Acc. 108334. A 49-year-old white man was dyspneic, cyanotic, cold, perspiring, and confused when admitted to the hospital. He had been ill for one week and bedridden for three days with pleural pain and fever. The temperature was 98°F. and there were physical signs of pneumonia in the right lung. Heart sounds were faint; the pulse was weak and rapid (146 per minute); the blood pressure was 90/60. Sulfadiazine was administered and oxygen given. Hemolytic streptocci were grown from the sputum. By the fourth day there was definite improvement. The pulse and heart action were better, cyanosis was no longer present, temperature was 99°F., and pulse was 100 per minute. Sulfadiazine was discontinued. Oliguria was noted on the ninth hospital day; also mental confusion and incontinence. The blood pressure was still low. The nonprotein nitrogen reached 130 mg. for each 100 c.c. of blood on the twelfth day and 214 mg. on the sixteenth day despite efforts to increase renal function. Urinalyses were characteristic of acute glomerulonephritis. Mental confusion and increasing weakness dominated the remainder of the

clinical course during which Cheyne-Stokes respirations and weak heart action were noted. Death occurred on the nineteenth day in the hospital.

CASE 12.—AIP Acc. 158943. A 28-year-old white man was admitted to the hospital with headache, backache, nausea, vomiting, and periorbital edema. He had scarcely recovered from an attack of acute nasopharyngitis which had originated two weeks earlier. The urinary findings indicated acute glomerulonephritis. The blood pressure measured 150/90. Oliguria, gross hematuria, edema, and increasing azotemia were associated with marked mental aberration. Treatment had included several transfusions of blood and plasma. Terminally, the nonprotein blood nitrogen measured 120 mg. per cent, and the patient died on the twentieth day in the hospital.

CASE 13.—AIP Acc. 148005. A 42-year-old white man had had his left leg amputated three weeks following the shattering of his ankle by a shell fragment. During the next month there was low-grade intermittent fever and mild diarrhea improved by a two and one-half week course of sulfadiazine. One and one-half months following the amputation, pneumonia developed rather suddenly. Though the temperature responded promptly to penicillin, dyspnea, cyanosis, dependent edema, and hydrothorax developed. The heart rate was raised and at times irregular. The urine which had been previously normal now contained large amounts of albumin and numerous red and white cells. Digitalis proved of no avail and the patient died four weeks after the onset of the pneumonia. Hypertension of unstated degree had been noted during the last month of illness.

CASE 14.—AIP Acc. 102428. A 20-year-old white man was admitted to the hospital with a five-day history of nasopharyngitis, a fever of 101°F., cough, constant "epigastric pain," and swelling of the hands and feet. Three weeks previously he had had an acute pyogenic infection of an epidermophytosis of the foot with fever of 102°F., lymphangitis, and swollen lymph nodes. This infection had been effectively treated with hot applications and with sulfonamides. The urinary picture indicated acute glomerulonephritis. Nonprotein nitrogen measured 35 mg. for each 100 c.c. of blood. Temperature ranged from 98° to 101°F. and pulse rate, from 100 to 120 per minute. Purpuric skin lesions occurred in successive crops. Epistaxis was observed on the tenth day; abdominal pain became more severe. On the eleventh day there was apathy and mental aberration. Death followed the sudden development of pulmonary edema on the twelfth day. White blood cell counts ranged between 9,600 and 14,600; differential counts and cell types were normal. Platelet counts, measurements of bleeding and clotting times, and prothrombin determinations failed to produce evidence to account for the purpuric manifestations.

CASE 15.—AIP Acc. 103282. A 30-year-old white man was hospitalized because of urinary evidence of acute nephritis. For one month previously there had been intermittent bouts of diarrhea, anorexia, nausea, and vomiting, treated with variable success with bismuth preparations, paragoric, and sulfaguanidine. On admission, the temperature was 90° F.; pulse, 58; blood pressure, 100/64; the blood urea nitrogen was elevated; and the leucocytes numbered 9,900. There was oliguria which progressed to anuria after the third day. Signs of mild pulmonary edema were found on the sixth day; an electrocardiogram was normal; the sedimentation rate was greatly accelerated. Treatment consisted of frequent intravenous instillations of fluids to induce diuresis. Death occurred on the eighth day after admission to the hospital.

CASE 16.—AIP Acc. 151123. A 32-year-old white man was admitted to the hospital with fever, sore throat, and cough of ten days' duration. The temperature was 100.6°F.; pulse rate, 80; respirations, 18 per minute; blood pressure, 138 80. Leucocytes numbered 4,300. Urinalyses showed albuminuria, hematuria, and casts. The course was persistently febrile with temperatures ranging from 101° to 104° Fahrenheit. Blood cultures were repeatedly sterile. Facial edema developed on the seventeenth day; cardiac enlargement was noted radiologically on the nineteenth day. Supportive treatment had included frequent transfusions of blood and plasma. Auricular fibrillation developed on the fortieth day and despite digitalization, death occurred three days later. Blood nitrogen determinations were repeatedly within normal limits, as were the blood pressures taken many times.

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ANEURYSM OF THE CORONARY ARTERIES

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IN 1929, Packard and Wechsler[1] observed a case of aneurysm of the left coronary artery with rupture. In reporting this they made an extensive search of the literature and found the earliest report of aneurysm of the coronary vessels to be that of Bougon[2] in 1812. In their review they eliminated all cases of periarteritis nodosa and apparently also eliminated those of "diffuse aneurysm," or generally dilated vessels, limiting the cases they considered bona fide to localized enlargements and thereby including only saccular and fusiform aneurysms. They considered that most cases they reviewed could be classified as either mycotic-embolic or arteriosclerotic. Their reason for calling the lattér group arteriosclerotic in type was merely the fact that all cases showed some atherosclerosis and there was no definite evidence to indicate what the exact origin was. Two bona fide cases of localized coronary aneurysm reported prior to 1929[3,4] were not included in their review. The case of Bristowe,[5] which they eliminated as being periarteritis nodosa, does not include sufficient data to verify this diagnosis clinically; microscopic description is lacking, and the author clearly indicates that there was no involvement in the other arteries of the body. However, this case will not be added to the present review.

Since their report, there has been an average of one report of coronary aneurysm annually, and the various authors have used the term "aneurysm" in its broadest sense, including all types of dilatations, as well as dissecting aneurysm, in enumerating the cases to date.

Recently, at the Mallory Institute of Pathology, an 84-year-old man was autopsied who had a coronary aneurysm which in size is unique in the annals of medical literature. It is the only case of this type which has been recorded at this institution, where there are 19,403 autopsies on file (Jan. 1, 1947). This case is reported herewith, and in order to clarify the present status of aneurysm of the coronary arteries a review of the literature since 1929 with tabulation of essential data has been made (Tables I and II).

Of the cases commonly mentioned and enumerated in recent reviews, two will be eliminated from further discussion. Schuster's report[6] was of an aneurysm of the sinus of Valsalva, involving secondarily the orifice of the left coronary artery, and no other portion of either coronary artery. Westerlund's case[7] had only an aneurysm of the left ventricular wall, which followed coronary occlusion

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TABLE I. CLINICAL AND PATHOLOGIC FINDINGS IN REPORTED CASES. THE CLASSIFICATION IS BASED ON STRUCTURE

	AUTHOR	AGE	SEX	PREVIOUS HISTORY	SYMPTOMS AND TYPE OF DEATH	SITE	SIZE	CORONARIES	OTHER PATHOLOGIC CHANGES
					Localized Aneurysms				
1	Abbott (1908)[3]	60	F	No cardiac symptoms (No other clinical data given)		Right coronary just distal to origin	"Crab-apple" 2.5 cm. above epicardium	Thick-walled, wide tortuous channels	Left coronary originated from pulmonary artery, and there were anastomoses with right coronary artery; flow was thought to be toward pulmonary artery
2	Trevor (1912)[4]	11	F	Onset of chills and fever 22 days before death Harsh tricuspid to-and-fro murmur 5 days before death. Blood culture: positive *Streptococcus viridians*	Died from sepsis	Right coronary, termination of a dilated portion	"Plum"	Right coronary dilated to 1 cm.	Aneurysm ruptured into right ventricle at inner side of anterior papillary muscle with organized thrombus at the site
3	Abbott and Chase (1929)[14]	34	M	Athlete, rejected for military service in World War I for "Athlete's Heart"; 1 year prior had had repeated colds and fainting episodes	4 weeks before death had chills and fever with emboli to hands and feet, precordial pain; died suddenly	Left circumflex	"Walnut"	Thrombosis in circumflex branch of left coronary distal to mycotic aneurysm	Aneurysm ruptured into left auricle; fibrohemorrhagic pericarditis; bicuspid aortic valve with vegetations which showed *Streptococci;* "false aneurysm" at base of heart, "hen's egg" in size
4	Cox and Christie (1930)[15]	65	M	Hypertension several years; dyspnea and edema 10 months, without response to digitalis and diuretics after first 2 months	Moribund several days before death, expired quietly	Right coronary, several cm. distal to origin	2.5 × 4.0 cm. (fusiform)	Markedly sclerotic	Right coronary anomalous; thrombosis left anterior descending branch with healed infarct; marked atherosclerosis of aorta, saccular aneurysm 11 cm. diameter

5	Vogelsang (1930)[16]	38	M	Compression injury to chest 3 months before death; pain on inspiration and pressure and prickling sensations in heart region thereafter	3 days before death began coughing up bright red sputum; died suddenly	Left coronary, anterior descending branch	6.0 × 5.5 × 4.5 cm.	Thickening of intima with obliteration of lumen, perivascular round cell infiltration, thrombosis distal to aneurysm	Gummata in right ventricular wall; gummatous myocarditis, periarteritis, and endarteritis with vascular fibrosis and plasma cell infiltration in connective tissue
6	Domenishini (1934)[17]	77	M	No clinical data given		Left coronary	"Nut"	Moderately sclerotic	Thrombosis in aneurysm and in vessel distally
7	Snyder and Hunter (1934)[18]			Clinical data unknown		Left coronary, 5.0 mm. from origin	3.5 × 2.0 × 1.0 cm.	Plasma cell and lymphocyte infiltration of walls with fragmentation of elastica	Syphilitic mesoaortitis with saccular aneurysm of ascending aorta, aneurysm of sinus of Valsalva lying next to coronary aneurysm
8	Eliasoph (1935)[19]	58	M	10 years of increasing dyspnea, orthopnea, and headaches; nocturnal dyspnea for 5 years; ECG showed myocardial damage	Cardiac decompensation with no response to digitalis and diuretics; gradually lost ground and expired quietly	Left coronary, 1.0 cm. distal to origin	7.0 mm.	Marked atherosclerosis	Many small coronary occlusions; large aneurysmal dilatation of left ventricle with degeneration of septum
9	Seydel (1935)[20]			No clinical data given		Left coronary, anterior descending branch	"Pea" ("Umgefahr Erbsengrosse")	Marked atherosclerosis	Scarring and fibrosis of myocardium; syphilitic aortitis
10	Rae (1937)[21]	2-9/12	M	Pale and listless for 1 month; joint tenderness, fever, lymphadenopathy; weak and had "blue spells" for 9-10 months	Fever to 101° F. that subsided, but leucocytosis with many immature forms persisted; sudden death	Left coronary Right coronary	1.5 cm. diameter 1.0 × 2.0 cm.	Exudative necrotizing reaction in vascular walls	Fibrinous pericarditis, thrombosis of aneurysm on right coronary, and rheumatic carditis
11	Chiari (1938)[10]	34	M	5 weeks' history of pain in chest and dyspnea with gradually increasing palpitation	Died of congestive failure	Right coronary, 5.0 cm. from origin	10.0 × 7.0 cm. with constriction in midportion	Slight atherosclerosis	Pulmonary artery compressed by aneurysm; right auricle and ventricle dilated; funnel-shaped origin of right coronary; no elastica in wall of aneurysm

TABLE I. CLINICAL AND PATHOLOGIC FINDINGS IN REPORTED CASES. THE CLASSIFICATION IS BASED ON STRUCTURE—CONT'D

	AUTHOR	AGE	SEX	PREVIOUS HISTORY	SYMPTOMS AND TYPE OF DEATH	SITE	SIZE	CORONARIES	OTHER PATHOLOGIC CHANGES
12	Manohar (1938)[22]	Adult	M	Penile lesion many years previously; aneurysm of abdominal aorta diagnosed by x-ray; pain in back and legs for 3 months	Rumbling systolic sound in 3rd left intercostal space; collapsed and died suddenly	Left coronary, just distal to origin	1.5 × 1.0 cm.	Gummatous changes in wall of aneurysm and general thickening of intima	Rupture of aneurysm of celiac artery; hepar lobatum; positive Kahn and Wassermann tests on post-mortem serum
13	DeNavasquez (1939)[23]			No clinical data given. Case is listed incidentally in a review of 20 hearts from proven cases of *Streptococcus viridans* subacute bacterial endocarditis		Left coronary, descending branch, halfway to apex	1.0 × 1.0 cm. (mycotic)	Occlusion of vessel proximal to aneurysm	Myocardial infarction of left ventricular wall
14	Chipps (1942)[24]	45	M	Rheumatic endocarditis 20 years previously; chills and fever 6 months; blood culture positive for *Streptococcus viridans*	Severe constricting pain in chest followed by gradual improvement for 10 days; then sudden death	Left coronary, anterior descending branch, 2.0 cm. from origin	1.9 × 1.6 cm. (mycotic)	Vessel occluded distal to aneurysm	Embolus to left pulmonary artery; heart weight: 660 grams; bacterial endocarditis on mitral valve; aortic stenosis
15	Rigdon and Vandergriff (1943)[11]	33	M	Sudden onset substernal pain 15 days before death; ECG showed evidence of left coronary occlusion with infarction	Developed acute respiratory distress with pulmonary edema and died 4 hours later	Left coronary Right coronary	2.0 × 1.5 cm. 1.0 × 2.0 cm. 1.0 × 2.0 cm. 1.0 × 2.0 cm.	Loss of elastica and thinning of muscularis in wall of aneurysm	Thrombosis of anterior descending branch, left coronary, just distal to aneurysm
16	Marano and associates (1945)[25]	43	F	Past history of rheumatic fever; negative Kahn and Wassermann; ECG evidence of myocardial damage	Gradual onset of dyspnea and palpitation over period of years; died in congestive failure	Right coronary	1.0 × 0.7 cm.	Slight atherosclerosis	Aneurysm ruptured; syphilitic mesoaortitis; plasma cell and lymphocyte infiltration of media and adventitia with loss of elastica and hyalinization

Diffuse Aneurysms

1	Halpert (1930)[26]	54	M	Pains in knee joints, no cardiac complaints	Died from carcinoma of stomach with metastases to liver	Right coronary	1.5 × 2.0 × 20 cm.	Slight atherosclerosis	Arteriovenous communication at termination of enlarged vessel
2	Nagoya and Takahashi (1932)[27]	72	M	Puny in childhood, but no complaints in later life until age 61 years when precordial pain, palpitation, and dizziness followed by dyspnea and cyanosis; joint pains at ages 63 and 68 years	Sudden precordial pain with dyspnea; edema and coma followed; died 1 day later	Left coronary, circumflex branch	1.0 to 1.8 × 21.5 cm.	Marked atherosclerosis	1.0 mm. opening into coronary sinus at termination of dilated vessel; mural thrombus in coronary sinus; recent infarct of left ventricle
3	Lowenheim (1932)[28]	62	F	Cardiac symptoms for 2 years, blood pressure up to 260/100	Gradually progressing congestive failure	Right coronary	2.0 cm. diameter for length of vessel	Vascular walls thickened	Heart weight, 835 grams; arteriovenous communication at termination of dilated vessel, veins also dilated
4	Kockel (1934)[29]	38	M	10-year history of precordial discomfort	Found dead; no information on immediate symptoms	Right coronary	0.6 to 1.2 cm. diameter for length of of vessel	Slight atherosclerosis	Left coronary originated from pulmonary artery, right coronary supplied entire heart with arterial blood
5	Harris (1937)[30]	43	M	No known cardiac symptoms	Died from hemorrhage into brain tumor	Right coronary	0.7 × 13 cm.	Slight atherosclerosis	Aneurysmal vessel is anomalous branch of right coronary which terminated directly into chamber of right auricle; remainder of right coronary not enlarged and had normal distribution

Miscellaneous Types (Dissecting)

	Pretty (1931)[8]	42	F	30 hours before death, onset of nausea and vomiting with pain in the chest	Was fairly comfortable and did not appear terminal, when death occurred suddenly	Right coronary	——	Atherosclerosis of all coronary vessels, with dissecting aneurysm on right	——

TABLE II. ETIOLOGIC CLASSIFICATION OF LOCALIZED ANEURYSMS

	ORIGINAL CLASSIFICATION			SUGGESTED REVISION							
	MYCOTIC-EMBOLIC	ARTERIO-SCLEROTIC	OTHERS OR UN-CLASSI-FIED	MYCOTIC-EMBOLIC	ARTERIO-SCLEROTIC	CON-GENITAL	SYPHI-LITIC	PURE MYCOTIC	RHEU-MATIC	PROBABLY PERI-ARTERITIS NODOSA	UNCLAS-SIFIED
Bougon	x			x							
Merat			x								x
Hedlund			x								x
Peste		x				x					
Peacock		x				x					
Heuse			x							x	
Finnell			x								x
Markoe			x								x
Wood		x				x					
Ogle	x			x							
Buchner		x				x					
Gee			x			x					
Crisp		x				x					
Malet and Evans			x			x					
Eppinger	x			x							
Clarke			x							x	
Capps		x				x					
Capps		x					x				
Griffith	x			x							
Griffith	x			x							
Toller	x ?			x ?							
Ruge			x					x			
Winkler		x			x						
Henke	x			x							
Somner		x				x					
Martland		x					x				
Fraenkel			x			x					
Lublin	x			x							
Windholz		x			x						
Packard		x			x						

Reported Subsequent to 1929 or Not Included in Above

Abbott			x					
Trevor	x							
Abbott and Chase	x							
Cox and Christie			x					
Vogelsang				x				
Domenishini		x						
Snyder and Hunter				x				
Eliasoph		x						
Seydel		x						
Rae						x		
Chiari			x					
Manohar				x				
DeNavasquez	x							
Chipps	x							
Rigdon and Vandergriff			x					
Marano, Baila, and Cardeza				x				
Scott			x					
	12	6	15	6	1	1	2	4

Classification of cases reported prior to 1929 is from data in table published by Packard and Wechsler.[1]

that had been preceded by carbon monoxide poisoning, with no aneurysm of the arteries.

In the accompanying Table I the reports are divided into two main groups according to structure: (1) Localized aneurysms, including saccular, fusiform, mycotic, and so forth, and (2) diffuse aneurysms, including all in which a vessel was generally increased in diameter.

Only one case cannot be satisfactorily classified in either of these groups. It is the case of dissecting aneurysm reported by Pretty[8] in which no mention is made of the size of the vessel. There is some question as to whether this case should be included; however, it is listed and data given to permit the reader to decide whether he chooses to count it.

Analysis of the thirty cases listed by Packard and Wechsler (including the one they presented) showed several interesting features: there was no particular age distribution; the condition was present much more commonly in men; about one-half of the cases had rupture of the aneurysm; and only three cases gave any history of trauma that might have been contributory and this was discounted. Only three patients showed an associated syphilitic mesoaortitis and seven gave a definite history of rheumatic fever, while one other had had rheumatic pains. Other medical complications were scarletinal nephritis, generalized arteriosclerosis, and "cardiac disease." They were unable to show any pathognomonic clinical findings on which to establish the diagnosis, and they observed that sudden death caused by rupture of the aneurysm (occurring fourteen times) was the most common cause of death, while gradual heart failure was a cause in others. They made the observation that aneurysms usually occurred in the first part of the vessel concerned, or at the bifurcation of vessels, and that the condition occurred singly much more frequently and involved the left coronary more often than the right.

Four possibilities as to etiology were discussed with the pathogenesis for these types discussed in some detail: mycotic-embolic, arteriosclerotic, pure mycotic, and traumatic. All the cases were classified in one of the first three groups or were unclassified. One was considered pure mycotic; seven were definitely mycotic-embolic, with another considered to be probably in this group; and twelve were thought to be arteriosclerotic. Of the remaining nine, two were considered to be probably periarteritis nodosa and seven were not classified, four of which had insufficient data for any attempt at classification. The remaining three were similar in many features to the arteriosclerotic, but occurred at the ages of 5, 7, and 20 years and showed no atherosclerosis.

The possibility of congenital aneurysm or of an aneurysm developing on the basis of congenital defects in structure of the vascular wall was not considered. Since their paper was written, Forbus[9] has advanced the idea that aneurysms of the cerebral arteries are probably usually on this basis. He demonstrated defects in coronary vessels as well as in cerebral vessels, although the former were much less common. Other authors[10,11] expressed the opinion that many coronary aneurysms are of similar origin. The case of Rigdon and Vandergriff[11] had multiple aneurysms, all located at points of bifurcation; as pointed out by Forbus,[9] this is the locality where fusion of the muscularis in embryonic life is

apt to be incomplete and it is here that the elastic lamina is weakest. In support of the concept that more of the cases of doubtful origin are due to some congenital defect rather than to an arteriosclerotic process is the fact that they have been found in cases with minimal atherosclerosis and have been seen as early in life as 5 years and as late as 84 years, with the youngest showing no appreciable atherosclerosis and the oldest showing minimal involvement. Another factor is the occasional presence of other associated congenital anomalies in the heart. Possibly it would be wiser to leave this large group as unclassified until further evidence can be obtained to indicate more definitely what the etiology is. However, it does not seem unreasonable to consider them as congenital unless definite evidence indicates otherwise. Doing so would leave unclassified only those cases in which information is too meager to eliminate them from other possible groups.

Against the concept that these aneurysms are of arteriosclerotic origin is the fact that they are often seen in vessels with minimal atherosclerosis; that there are not uniformly atheromas at the sites of the aneurysms; that the aneurysmal walls often have well-localized, circumscribed, calcareous deposits within them, and these do not appear to be causing any disruption of the continuity of the vessel walls; and that some previously classified as arteriosclerotic were as large as 6.0 cm. in diameter, which seems a rather excessive degree of dilatation for a sclerotic vessel without the formation of a "false aneurysm" by rupturing into the surrounding tissue. Also one would expect to find some of these "false aneurysms," as well as the incidence of rupture, if the dilatation were due to destruction of the vascular wall by a degenerative process such as atherosclerosis. Furthermore, the average age of the patients classified by Packard and Wechsler as arteriosclerotic, which was 57 years, would be expected to be associated with a high incidence of atherosclerosis no matter what the etiology of the aneurysm. Most cases of this group on which microscopic studies have been made showed loss or diminution of the elastic lamina and replacement of the muscular fibers in the media by collagen, but very little mention is made of the presence of atheromas in the larger aneurysms.

Another etiological factor which received little consideration by Packard and Wechsler was syphilis, although three of the cases, including their own, showed associated syphilitic aortitis, and one of these showed involvement of the aortic valve. They considered syphilis as a possible factor in these cases but discounted it in favor of arteriosclerosis. One of these, reported by Martland[12] and considered to be syphilitic by him, was 6.0 cm. in diameter and was associated with an aortic aneurysm, as well as a syphilitic mesoaortitis, while the coronaries were not particularly atheromatous. Since their paper was written, Moritz[13] has demonstrated definite syphilitic endarteritis of coronary arteries as far as 12 mm. from the aorta.

It is not intended in this discussion to imply that atherosclerosis is not to be considered an etiological factor in the formation of aneurysms of medium-sized arteries. However, it does seem worth while to raise the question of how large a true aneurysm can be attributed to this condition and whether definite evidence in regard to degree of atherosclerosis should not be required before considering it to be of etiological significance. In view of this discussion, the data

on the cases reviewed by Packard and Wechsler have been examined and a reclassification suggested as in the accompanying table (Table II), considering as arteriosclerotic only those cases which are associated with a high degree of atherosclerosis at the site of the aneurysm.

Combining the data from previous reports with that of the case herewith reported, certain observations seem worthy of comment. In all there have been forty-six cases of localized aneurysms of the coronary arteries reported, and the present case brings the total to forty-seven.

SURVEY OF DATA

Type.—The most common type appears to be the congenital, with fifteen being so classified. The next in frequency are the mycotic-embolic, with eleven definite and one probable, for a total of twelve. There have been six arteriosclerotic and six with evidence to indicate syphilis as the most significant etiological factor. One was the result of acute rheumatic fever and one was purely mycotic. Two were probably periarteritis nodosa, but could not be eliminated from the series because the reports contained no description of the histology, and there was no other information on which to make this diagnosis. Four cases must remain unclassified because of insufficient data.

Since 1929, there have been reported five diffuse aneurysms of coronary vessels, all of which seem to have been of congenital origin. Three of these were associated with arteriovenous communications and one showed a connection directly into the right auricle, while the other was a right coronary artery that furnished the entire arterial blood supply to the heart, because the left originated from the pulmonary artery.

One dissecting aneurysm of the right coronary artery has been reported.

Location.—Of the forty-seven cases with localized aneurysm, the location in three is not specified. In the remaining forty-four, twenty-seven involved the left coronary only, eleven involved the right only, and six showed involvement of both. Thirty-six were single and eight were multiple, the remaining three being presumably single.

In the group with diffuse aneurysm, the right coronary artery was affected in four, while the left coronary was affected in only one.

The one case of dissecting aneurysm was of the right coronary artery.

Age.—(Based on the cases in which age was given by the author.) In the congenital group, fourteen patients ranged in age from 5 to 84 years, and the average was 47.1 years. Nine cases in the mycotic-embolic group occurred between the ages of 11 and 45 years, with an average of 29.7 years. Five aeriosclerotic aneurysms occurred between the ages of 58 and 77, the average being 65 years. Four patients in whom syphilis was a factor were between the ages of 32 and 43, with the average being 38 years. In the remaining cases in these groups, the age of the patient was not stated.

Sex.—In the fifteen congenital cases, fourteen patients were men and one was a woman. In the mycotic-embolic group, where the sex was known, six were men and four were women. Of the arteriosclerotic group there were four men and one woman, while in the syphilitic group there were three men and two women. Of the others, there were four men, three women, and in five cases the sex of the patient is not known. While these figures are not statistically significant, it is of interest to note that among the infectious types the ratio was three men to two women, whereas in the others the men were in great preponderance.

Cause of Death.—The commonest cause of death in the cases of localized aneurysm reported prior to 1929 was rupture of the aneurysm, but this complication developed only twice since then. The commonest cause of death since 1929 has been coronary thrombosis, which occurred nine times. In all but one of these,[15] either the aneurysm or the vessel distal to it was thrombosed. Chronic congestive failure occurred in three cases, including the case of Cox and Christie, which had coronary occlusion. Death was due to rupture of an abdominal aneurysm in one[22] and to complications from carcinoma of the prostate in one (present report). In two[13,14] the complete protocols were not available and the findings in the hearts did not adequately explain the deaths.

Clinical Features.—There were no clinical findings which would suggest an aneurysm of the coronary arteries. The symptoms, when there were any present, were those associated with coronary occlusion, with chronic heart disease, or sudden death took place.

CASE REPORT

W. L. (Hospital No. 1,213,451), an 84-year-old white man, was admitted to the Boston City Hospital on Aug. 5, 1946, with acute urinary retention. His past history revealed no illnesses of any consequence and he denied symptoms referable to other systems. Physical examination revealed nothing significant except a distended bladder and an enlarged, nodular, indurated prostate. The lungs were slightly emphysematous and the heart was not enlarged to percussion. The heart sounds were of good quality, without murmurs. The temperature was 100° F.; pulse, 95; respirations, 22; and the blood pressure, 120/70. Serologic test for syphilis (Hinton) was negative on Aug. 5, 1946. A clinical diagnosis of carcinoma of the prostate was made.

On preoperative chest x-ray study he was found to have a large, globular shadow on the right border of the heart (Fig. 1). At fluoroscopy this was seen to pulsate and the esophagus was displaced posteriorly and to the left (Fig. 2). A diagnosis of probable aneurysm of the right auricle was made. An electrocardiogram showed premature auricular beats and a shifting pacemaker, but was otherwise within normal limits (Fig. 3). X-ray films of kidney, ureters, and bladder, as well as an intravenous pyelogram, were normal except for an enlarged bladder.

Since he was asymptomatic from the cardiac viewpoint, it was deemed safe to proceed with surgery, and on Aug. 14, 1946, a bilateral orchidectomy was performed under local anesthetic. He had practically no reaction and on Aug. 22, 1946, a transurethral prostatic resection was done under spinal anesthesia.

Preoperatively his blood nonprotein nitrogen had been 37 mg. per 100 c.c., and immediately postoperatively it was 31. He responded well for eight days following the operation. At that

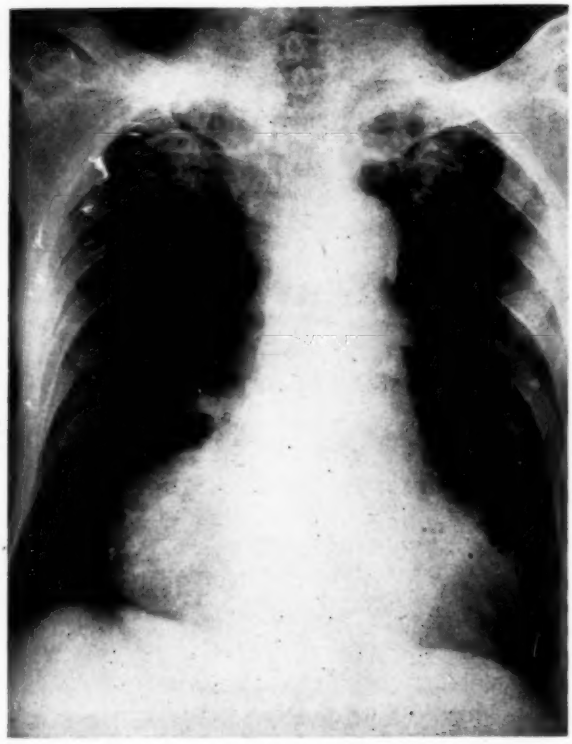

Fig. 1.—(W. L. No. 1,213,451). X-ray of chest taken at seven feet, showing large, globular mass extending to right of heart.

time he became somewhat stuporous and his blood nonprotein nitrogen was found to be 101 mg. per cent. During the following ten days this fluctuated, but gradually rose to 170; the carbon dioxide combining power dropped to 11 volumes per cent and he died in coma on Sept. 9, 1947.

At no time did he have any complaints referable to the heart or chest.

Clinical Diagnoses.—Carcinoma of prostate. Terminal uremia. Bronchopneumonia. Auricular aneurysm.

Autopsy.—(A46-473.) Performed Sept. 9, 1946, eight hours post mortem. The anatomic diagnoses were: (1) adenocarcinoma of the prostate with local invasion; (2) chronic cystitis with hydroureters; (3) severe bilateral acute pyelonephritis; (4) arteriosclerotic heart disease, mild; (5) anomalous coronary circulation with multiple aneurysms; (6) bronchopneumonia, both lower lobes; (7) fibrous pleural adhesions, left; (8) diverticulosis of colon and sigmoid; and (9) hepatitis, early, acute suppurative with focal necrosis.

On opening the chest cavity the heart was seen to be enlarged to the right. The enlargement consisted of a firm, globular mass measuring 10 by 8.0 by 8.0 cm. (Fig. 4), which on section was found to contain a laminated blood clot with fresh blood at the center of the laminations (Fig. 5). There were multiple small, saccular areas on the surface of the heart at the base of the aorta and pulmonary artery. There was another mass, 3.0 by 2.0 by 1.8 cm., on the anterior surface of the larger one. The myocardium was not remarkable except for a few scattered strands of fibrosis. The epicardium and the endocardium were not remarkable. The valves were thin and pliable. Heart weight: 780 grams. The wall of the right ventricle was 0.2 to 0.3 cm. in thickness; that of the left ventricle, 0.8 to 1.5 centimeters. Circumferences of valve rings were: tricuspid, 13.0 cm.; pulmonary, 8.5 cm.; mitral, 12.0 cm.; and aortic, 8.0 centimeters.

Fig. 2.—(W. L. No. 1,213,451). X-ray of chest with barium in esophagus, showing displacement to the left.

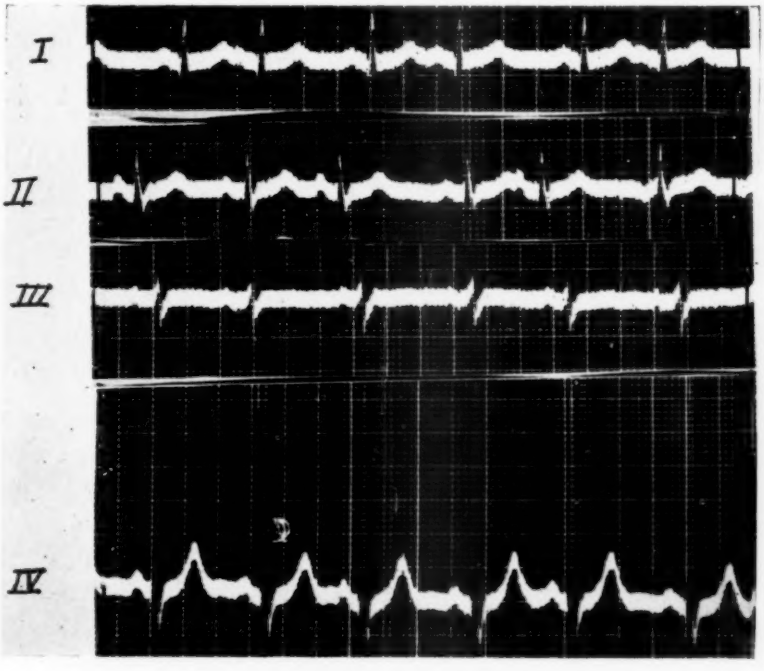

Fig. 3.—(W. L. No. 1,213,451). Electrocardiograph showing premature auricular beats and shifting pacemaker.

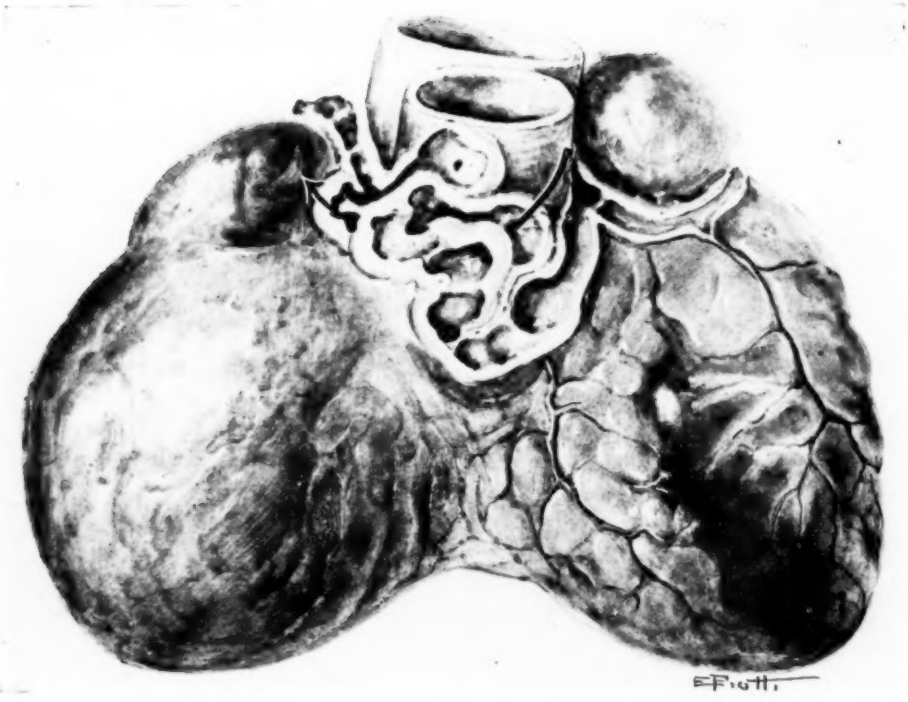

Fig. 4.—(W. L. No. 1,213,451, A46-473). Drawing of heart showing anterior view with large aneurysm to left. Anomalous vessel connecting anterior descending branch of left coronary to accessory right coronary is shown in detail. (Compare with Fig. 6.)

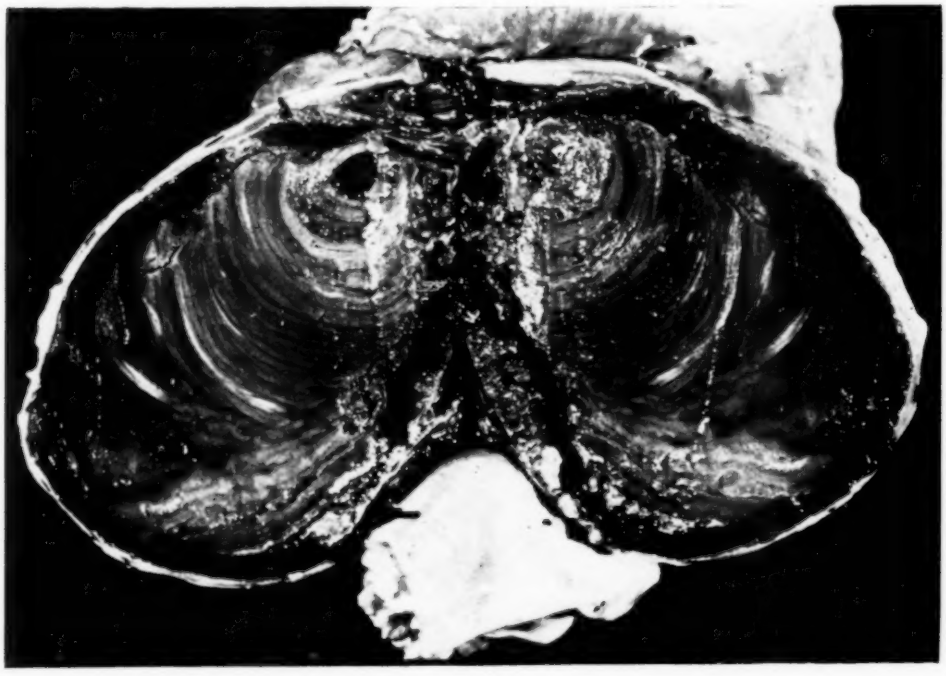

Fig. 5.—(W. L. No. 1,213,451, A46-473). Section through large aneurysm showing concentrically laminated thrombus with fresh blood at the center of laminations.

In dissecting the coronary arteries (Fig. 6) there were found to be two ostia in the right sinus of Valsalva and one in the left. These were not remarkable in appearance. From the right, one entered a vessel that followed the usual course of the right coronary artery, and was not remarkable except for a few atheromatous plaques. The other entered a vessel which proceeded 3.1 cm. anteriorly into the aneurysm measuring 10 by 8.0 by 8.0 cm., from which it emerged and, following a tortuous course, entered the aneurysm which measured 3.0 cm. in diameter. The vessel then went through four small, saccular enlargements (ranging from 0.3 to 0.7 cm. in diameter), received a communicating branch from the anterior descending branch of the left coronary, and terminated in a saccular dilatation, 1.6 cm. in diameter, which connected with the pulmonary artery through an opening not quite 2.0 mm. in diameter.

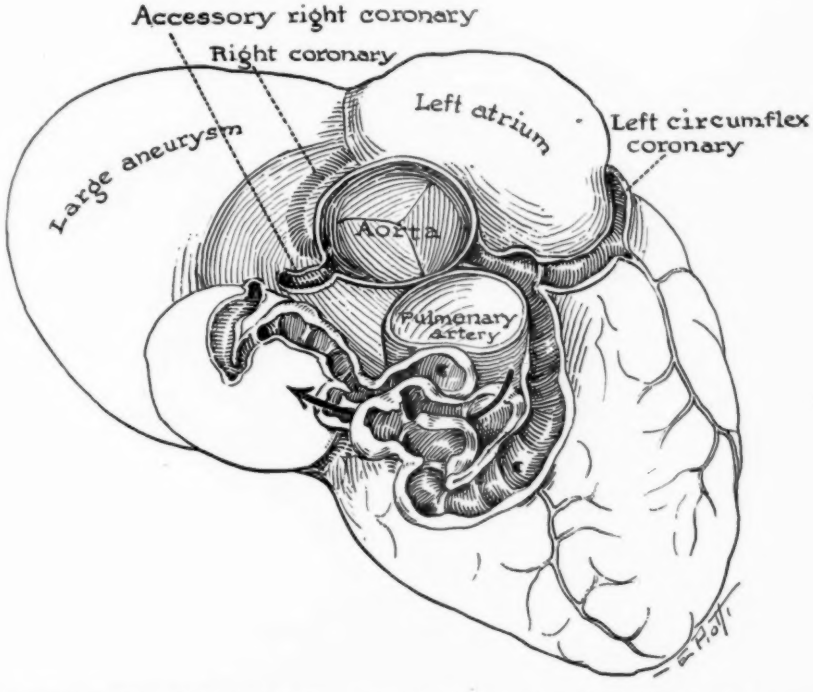

Fig. 6.—(W. L. No. 1,213,451, A46-473). Diagram of anomalous circulation showing connections to all aneurysms. The large aneurysm on the left of the picture overlies the right atrium which is obscured from view.

The left coronary artery proceeded 1.5 cm. from its origin to its point of bifurcation, where there was a small, saccular dilatation 0.8 cm. in diameter. The circumflex branch was not remarkable. The anterior descending branch was dilated to an inside diameter of 0.6 cm., and, 1.8 cm. distally, showed a saccular dilatation 1.1 cm. in diameter, from which two vessels emerged. One was 2.0 mm. in diameter and followed the usual course of the anterior descending coronary. The other was 3.5 mm. in diameter and followed a tortuous course, looping around and beneath itself (Figs. 4 and 6), eventually communicating with the accessory right coronary as has been described. Throughout its course it consisted of a series of localized dilatations with constrictions separating them.

From the origin of the left coronary to the communication with the branch from the right coronary artery, there were ten small dilatations ranging from 0.4 to 1.1 cm. in diameter. There were seven dilatations ranging from 0.3 to 10 cm. in diameter on the accessory right coronary artery. Thus, there were in all seventeen saccular dilatations ranging in size from 0.3 to 10 cm.

in diameter, and all were on the course of the anomalous circulation. These were entirely beneath the epicardium and, with the exception of the two largest, their lumina were patent. There were a few scattered atheromatous plaques on the walls and some of these appeared to be calcified. The walls of the smallest aneurysms were thin and translucent in some areas, measuring less than 1.0 mm. in thickness. The wall of the 3.0 cm. aneurysm was fibrous and calcific, measuring 2.0 mm. thick, and the wall of the 10 cm. aneurysm was fibrous, measuring 1.0 to 2.0 mm. in thickness.

In the remainder of the autopsy significant findings were present in the lungs, genitourinary tract, and the liver. There was also a diverticulum of the duodenum, 3.0 cm. in length and 1.0 cm. in diameter, as well as multiple shallow diverticula of the colon and sigmoid.

The left pleural cavity was completely obliterated by dense fibrous adhesions. The lungs were well aerated in the upper lobes, but both the lower lobes were very moist and firm. The right lung weighed 920 grams and the left, 780 grams. The dependent portions presented a nodular, mottled, reddish-purple appearance from which, on cut section, frothy, pinkish exudate could be expressed.

In the genitourinary tract the remaining prostatic tissue was nodular and firm, measuring 5.2 by 4.1 by 3.0 cm., and was adherent to the rectal wall and bladder wall. The seminal vesicles were shrunken, fibrotic, and hardly distinguishable from the prostate. The prostatic urethra was patent, but its surface was covered with a layer of purulent exudate. The bladder wall was thickened to 0.3 to 1.3 cm. and the lumen was filled with yellow, purulent material. The trigone was ulcerated and covered with exudate. The ureteral orifices were involved in the prostatic mass, but a 2.0 mm. sound could be introduced with some difficulty. Both ureters were dilated, measuring 0.8 cm. in diameter, and the walls were congested and grayish-green in appearance.

The right kidney weighed 260 grams and the left, 300 grams. Both were soft and the surfaces were studded with circumscribed, whitish-yellow masses which showed a tendency to coalesce. On cut section the parenchyma appeared reddish-brown with multiple abscesses measuring up to 1.0 cm. in diameter. There was poor corticomedullary differentiation, the cortex measuring approximately 0.8 cm. in thickness. The pelves and calices were filled with necrotic material which was greenish-yellow on the right and reddish-brown on the left. In the left kidney some of the papillae appeared darker brownish and had a necrotic consistence.

The liver weighed 2,020 grams. On the surface it was not remarkable, but on cut section it showed multiple, poorly defined, irregular areas which were greenish in the centers and shaded through yellowish zones to normal appearing liver tissue. These measured 0.5 to 1.0 cm. in diameter and tended to coalesce, forming irregular, serpentine patterns.

There were no other anomalies found and no other aneurysms. The brain was not examined. The aorta showed very slight atherosclerosis and there was a fibrous connection between the arch of the aorta and the pulmonary artery in the usual location for the obliterated ductus arteriosus.

Microscopic Examination.—Heart: The myocardium showed only a few scattered areas of interstitial fibrosis. The walls of small aneurysms were composed largely of collagenous tissue with fragments of elastica remaining and small deposits of calcium in the subintimal region; there was no muscular tissue. The walls of medium-sized aneurysms were made up of collagenous tissue with deposits of calcium beneath the intima. No elastic tissue and no muscle tissue could be seen and there was no differentiation into layers. There was an organizing thrombus on the surface of intima. The wall of the large aneurysm (10 by 8.0 by 8.0 cm.) was composed of collagenous tissue. No elastic tissue, no muscle tissue, and no differentiation of layers could be seen. Organization of thrombus was present on the surface of intima.

Lungs: In the lower lobes there was peribronchial acute inflammatory reaction extending into adjacent alveoli. The alveoli were partially filled with acute inflammatory exudate and with acidophilic homogeneous material.

Liver: Irregular areas of early necrosis of liver cells surrounded by slight inflammatory reaction, and containing collections of bacteria in the centers were present.

Kidneys: Diffuse, widespread, acute inflammatory reaction involving glomeruli, tubules, and interstitial tissue were present. There was a slight tendency to focal abscess formation. The tubules were moderately dilated. Vessels were engorged and there was intimal thickening of arterioles. There was some extravasation of blood in medullary portions.

Ureters and bladder: The epithelium was destroyed and there was invasion of underlying tissue by polymorphonuclear leucocytes. In some regions of the ureters, this extended through to the periureteral fat.

Prostate: There were irregularly shaped acini with areas of small, irregular cells containing scant cytoplasm and small, dark nuclei. A few mitotic figures and rare gaint cells were seen. There was stromal and perineural invasion by these anaplastic cells. A few scattered foci of acute inflammation were present.

Aorta: The structure was well preserved, with a few typical atheromas beneath the intima. There was no disruption of elastic tissue, even directly below atheromas.

DISCUSSION

This case showed three noteworthy features: the anomalous coronary circulation, the multiple aneurysmal dilatations on this portion of the coronary circulation, and the size attained by one of these aneurysms.

The developmental history of the anomaly is very difficult to analyze. As was shown by Grant,[31] the buds for the coronary vessels begin to develop at the stage of the 11.5 mm. embryo in rabbits, which is at the time the truncus communis is being separated into the aorta and pulmonary artery. Most of the anomalies of coronary circulation reported in the literature (as reviewed by Bland and associates[32]) consist of a displacement of the origin of one or the other of the main coronary arteries. These are easily explained by postulating a slightly abnormal location for the primordial vascular bud. However, in this case there was an abnormal direct communication between the left coronary artery and an accessory right coronary artery; and the common vessel thus formed communicated with the pulmonary artery. It is conceivable that this connection may have served as an accessory ductus arteriosus in embryonic life and persisted. However, there was a well-defined fibrous cord at the usual location for the ductus arteriosus, and it would seem likely that an accessory ductus would be obliterated in much the same manner as the main ductus. A search of the literature fails to reveal any case in which the disturbed circulation of the heart was comparable. The specimen reported by Abbott[3] showed a displacement of the origin of the left coronary artery, the origin being attached to the pulmonary artery and having anastomoses with the right coronary artery. The blood flow was thought to be toward the pulmonary artery in that case.

With the knowledge we have of normal pressure relations in the aorta and pulmonary artery, it is only reasonable to postulate that in this case the flow of blood was toward the pulmonary artery. On the basis of hydrodynamic principles it is further reasonable to postulate a slight actual flow. The friction to be encountered in the course of a vessel this length and having the tortuosity and other obstructions this vessel presented would materially reduce the effective pressure at the site of entrance into the pulmonary artery. This is borne out by the fact that the opening at the pulmonary artery was relatively much smaller than most of the remainder of the vessel. This also gives us a basis for speculating on the development of the aneurysms.

The pressure transmitted from the aorta was opposed by a lesser pressure from the pulmonary artery, but the length of the vessel and its tortuosity tended to equalize these pressures at the level of the pulmonary artery. The result

was an absorption of the aortic pressure by the walls of the anomalous vessel, with dilatation at its weakest points.

The largest aneurysm itself is unique in regard to size. Chiari[10] reported one that was almost as large, but it had a constriction making it somewhat hourglass shaped. In his case the patient died from constriction of the pulmonary artery by pressure from the aneurysm, which led to chronic congestive failure.

The significance of this condition does not seem great when we consider that at no time were there any cardiac symptoms and that the patient survived to the age of 84 years, finally dying from complications of carcinoma of the prostate. In a different location, the aneurysm could have caused symptoms from mechanical effects, as in Chiari's case. With a greater tendency to hypertension, the patient may have died at a much younger age from a rupture of one of these sacculations. There was also the possibility of coronary occlusion from thrombosis in one of the two aneurysms located along the course to the left anterior descending coronary artery. Since none of these occurred, the case is of particular interest as an illustration of the extent to which an abnormality can be present in the heart without causing symptoms.

SUMMARY

1. The literature on aneurysm of the coronary arteries is reviewed.

2. It is suggested that aneurysms of the coronary arteries be considered as either localized or diffuse; and that the localized be further classified into four main groups: congenital, mycotic-embolic, syphilitic, and arteriosclerotic. All diffuse aneurysms of the coronary arteries appear to be on a congenital basis.

3. Using this classification, a total of forty-seven localized aneurysms have been reported since the first report in 1812; and these may be divided as follows: fifteen congenital, twelve mycotic-embolic, six syphilitic, six arteriosclerotic, four of other types, and four unclassified.

4. The common complications of the condition are rupture, thrombosis, and associated myocardial disease.

5. When a localized aneurysm occurs, the left coronary artery is the more frequently involved and the condition is usually single.

6. In a diffuse aneurysm, the right coronary artery is more commonly affected.

7. There are no pathognomonic clinical findings.

8. Men are much more frequently affected than women, particularly in those aneurysms of congenital origin in which the ratio is 14:1.

9. A case is presented in which there were no cardiac complaints in life, and at autopsy there was found an anomalous coronary circulation with multiple aneurysms, the largest of which measured 10 by 8.0 by 8.0 centimeters.

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ATRIAL INFARCTION WITH DIAGNOSTIC ELECTROCARDIOGRAPHIC FINDINGS

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THE purpose of this report is to present a case of myocardial infarction in a 61-year-old man in whom the correct ante-mortem diagnosis of atrial infarction was made on the basis of typical electrocardiographic changes.

Prior to the report of Cushing and associates,[1] the true incidence of atrial infarction was generally unrecognized. Their study showed that the atria were involved in thirty-one (17.0 per cent) of 182 cases of myocardial infarction proved at autopsy. Previous reports[2-4] had indicated a much lower incidence, probably because the atria were not routinely examined adequately and specifically for infarcts. The clinical recognition of atrial infarction is still uncommon, as judged from the paucity of reported cases.[1,3,5,6] The importance of atrial infarction rests on the sequelae, that is, concomitant mural thrombosis in 80 to 84 per cent of the cases,[1,7] with pulmonary thromboembolism in 24 per cent,[8] rupture,[4,9-12] disturbances of conduction which may persist after the acute episode,[6] and arrhythmias such as auricular fibrillation, auricular flutter, and premature auricular beats.[3]

A high incidence of rupture of hemorrhagic infarcts of the atria, especially of the right, has been reported. Clowe and co-workers[9] analyzed fifty-four proved cases and found rupture in right atrium in 70 per cent of them. Krumbhaar and Crowell[4] reviewed 632 reported cases of rupture of the heart; the right atrium was involved in 5 per cent and the left, in 2 per cent. We are reluctant to accept these figures as indicative of the true incidence of atrial rupture, since there were no cases of rupture in the well-studied series of Cushing and associates.[1] It is probable that the incidence of rupture is much lower, because the true incidence of atrial infarction was not realized until recently.

CASE REPORT

H. C., a 61-year-old white man, was admitted to Michael Reese Hospital on Nov. 12, 1946, with the chief complaint of chest pain and syncope. On the morning of admission, while in the Cardiac Clinic, the patient suddenly experienced sharp precordial pain which radiated to the middle of the back. He became nauseated and dizzy, collapsed, and lost consciousness for several minutes.

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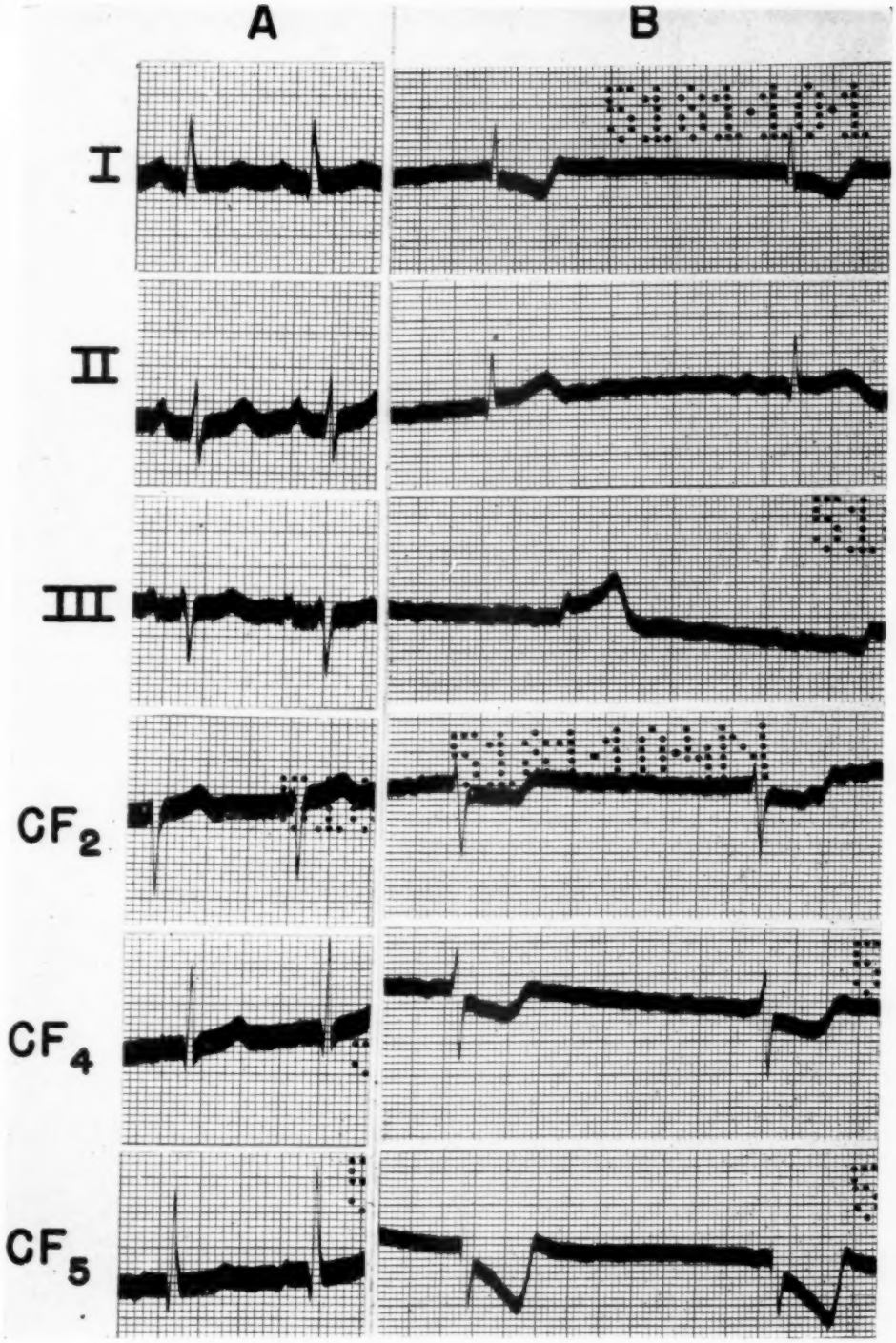

Fig. 1.—*A*, Five months before present illness. Sinus rhythm, left axis shift. *B*, First hospital day. Coarse auricular fibrillation with complete A-V block with the idioventricular pacemaker arising above the bifurcation of the common A-V bundle. Recent posteroseptal infarct.

For the past three years the patient had been treated for hypertension, angina pectoris, and mild diabetes mellitus which had been controlled by diet alone. In 1930, the patient had pulmonary tuberculosis and spent six months in a sanatorium. There were three previous hospital admissions. In October, 1945, he was hospitalized for an acute exacerbation of chronic cholecystitis, fibroid pulmonary tuberculosis, bronchiectasis, and senile emphysema. In February, 1946, he had an hemoptysis. The source was not definitely determined, but it was thought to be from the cavity in the right lung. In May, 1946, the patient was again hospitalized for an exacerbation of chronic cholecystitis. Cholelithiasis was found upon roentgen examination. Cholecystectomy was advised after convalescence.

On admission, the patient appeared acutely ill, cyanotic, and in obvious shock with a cold, clammy skin. The blood pressure was 108/60, the pulse rate was 44, the respirations were 25 per minute, and the temperature was 99.8° Fahrenheit. The pupils were equal and reacted to light and near vision. The neck veins were markedly distended and pulsating. Moist râles were heard in both lung bases. The heart was enlarged to percussion. The heart sounds were distant. No murmurs were heard. The radial pulse was weak, slow, and regular. The liver, kidneys, and spleen were not palpated.

The immediate supportive therapy consisted of morphine, atropine and aminophylline. The blood pressure rose to 174/100 within twelve hours. The pulse rate increased to 90 per minute, and the pulse was of better quality. However, on the second hospital day, the blood pressure again fell and remained in the vicinity of 114/60. On the third hospital day, the pulse rate was 56 and grossly irregular. The patient was conscious and mentally alert throughout his hospital course. The temperature varied from 99.6 to 100.2° Fahrenheit. On the sixth day, the patient suddenly became pulseless and died within several minutes.

Electrocardiograms.—An electrocardiogram made on July 17, 1946 (Fig. 1,*A*), five months before the present illness, showed sinus rhythm and left axis shift. This tracing was considered to be probably abnormal because of the absence of R in Lead CF_2. Fig. 1,*B* shows the electrocardiogram made on the first hospital day; there was coarse auricular fibrillation with complete A-V block, with the idioventricular pacemaker arising above the bifurcation of the common A-V bundle. Changes in the S-T segments and T waves suggested a very recent posteroseptal infarct.

The electrocardiogram shown in Fig. 2,*A* was taken on the morning of the second hospital day. The mechanism now was a regular sinus rhythm with first degree A-V block. Fig. 2,*B* was taken on the evening of the second hospital day. Now there was second degree A-V block with the A-V ratio varying between 3:1 and 3:2. The ventricular rate was 65 per minute, the auricular rate, 100. Changes in the S-T segments and T waves were less marked in all leads.

Fig. 3,*A* shows the electrocardiogram taken on the fifth hospital day. It shows a sinus rhythm and complete A-V block with the idioventricular pacemaker arising above the bifurcation of the common A-V bundle. The elevation of the $P\text{-}T_A$ segment in Leads II and III and the changing auricular mechanism were considered compatible with atrial infarction.

The electrocardiogram shown in Fig. 3,*B* was taken twelve hours before death. The ventricular rate is slower in this record. The elevation of the $P\text{-}T_A$ segment in Leads II and III persists.

Autopsy.—Post-mortem examination revealed coronary arteriosclerosis with (a) recent thrombosis of the main right coronary artery, (b) old arteriosclerotic occlusion of the left circumflex and left anterior descending rami, (c) massive recent infarct superimposed upon old infarct of the interventricular septum and posterior wall of the left ventricle, with acute fibrinous pericarditis, and (d) recent infarct superimposed upon an organizing infarct of the posterior wall of both atria, with acute fibrinous pericarditis. In addition, there were chronic passive hyperemia of the lungs, liver and kidneys, arteriosclerosis of the kidneys, fibrocaseous tuberculosis of the apex of the right lung, and chronic cholecystitis, pericholecystitis, and cholelithiasis.

The heart weighed 400 grams. The left ventricular wall measured 1.5 cm. in thickness; the right, 0.3 centimeter. The tricuspid ring measured 13 cm. in circumference; the mitral, 9.0 cm.; the pulmonary, 8.0 cm.; and the aortic, 7.0 centimeters. The epicardium on the posterior

aspect was dull and finely granular. The endocardium was smooth and glistening except on the posterior wall of the left ventricle where it was dull, white, and thickened. The myocardium of the posterior wall and upper posterior one-third of the interventricular septum was soft and flabby and was the seat of recent infarction. In this region the pattern of myocardial fibers was poorly outlined, and there were numerous gray and bright yellow friable areas interspersed with hemorrhagic ones. The infarct measured approximately 5.0 by 6.0 cm. and was sharply delineated from the surrounding reddish-brown, firm myocardium.

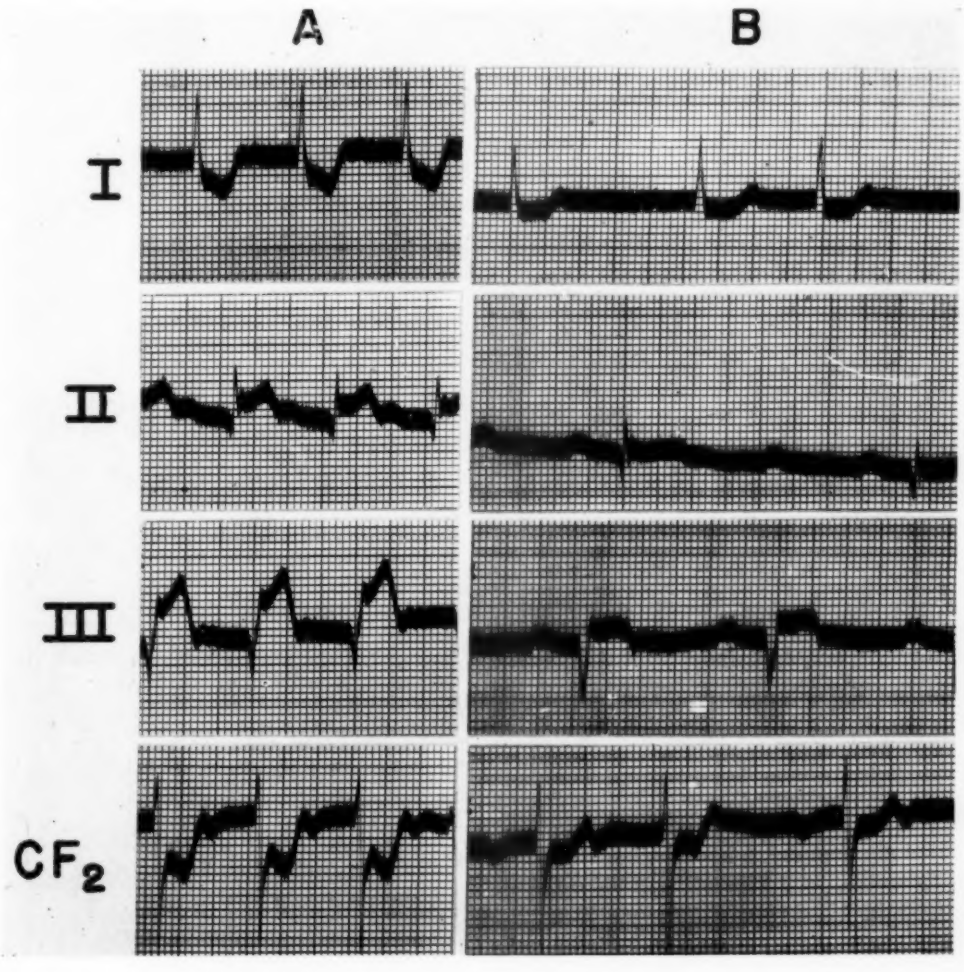

Fig. 2.—*A*, Morning of second hospital day. Sinus rhythm, first degree A-V block. *B*, Evening of second hospital day. Second degree A-V block.

Upon multiple transections of the atria, a soft area was found involving the posterior wall of both atria. The atrial myocardium in this region was friable and red mottled with yellow. This area measured 3.5 by 2.0 cm. and was astride the atrial septum, above and parallel to the auriculoventricular sulcus. Loosely attached to the endocardium in this region were small, red, fibrinous thrombi. The superjacent atrial epicardium was dull, finely granular, and roughened. The right coronary artery was predominant. The coronary arteries were rigid, pipestem, and

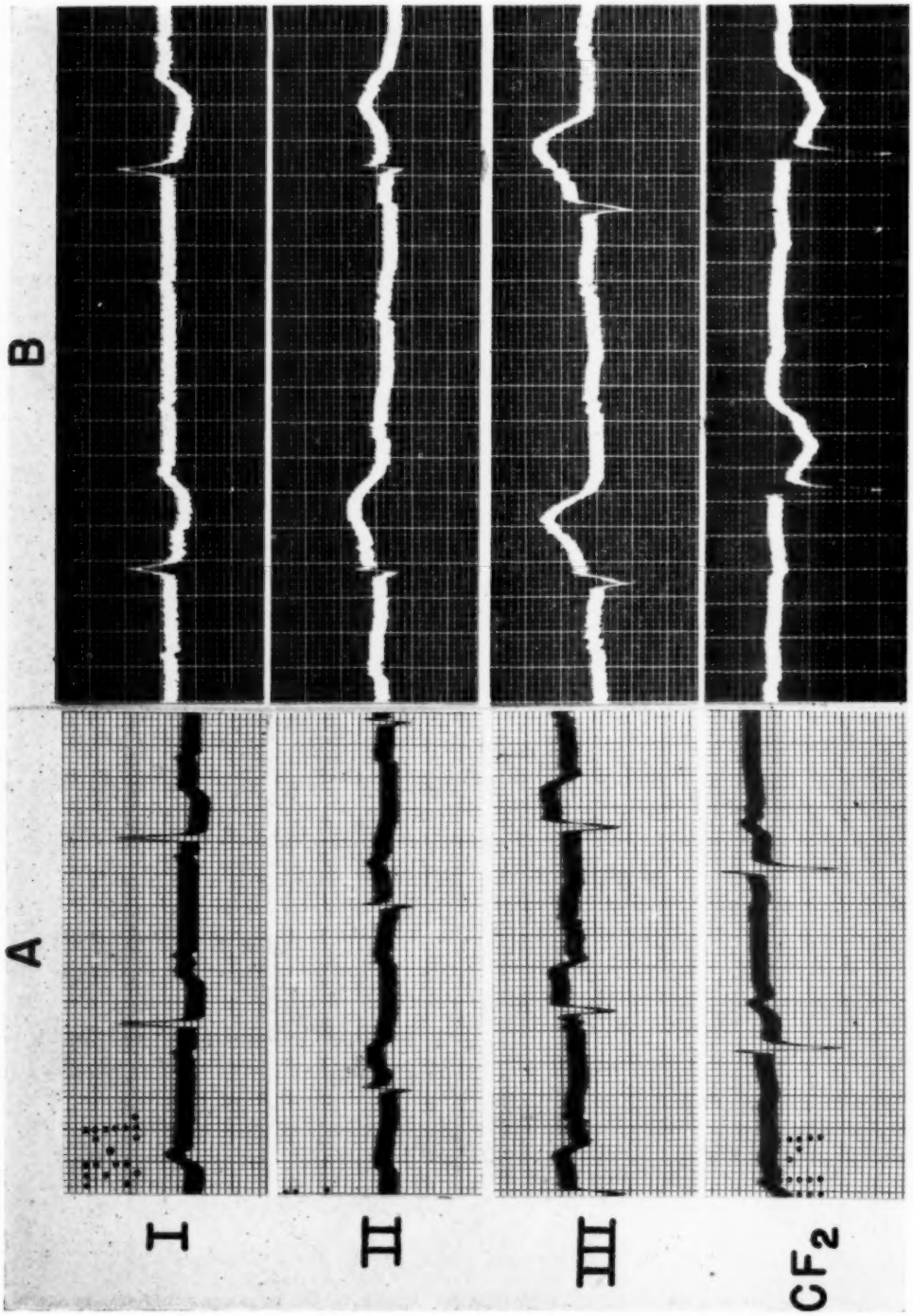

Fig. 3.—*A*, Fifth hospital day. Sinus rhythm. Complete A-V block. Note elevation of P-T$_A$ segment in Leads II and III. Changing auricular mechanism and displacement of the P-T$_A$ segment compatible with atrial infarction. *B*, Twelve hours before death. Elevation of P-T$_A$ segment in Leads II and III persists.

contained numerous arteriosclerotic plaques. The left anterior descending branch was markedly narrowed by a calcific intimal plaque 2.0 cm. below its origin. There was a similar stenosis of the lumen of the left circumflex branch 3.0 cm. from its origin. The lumen of the right main

Fig. 4.

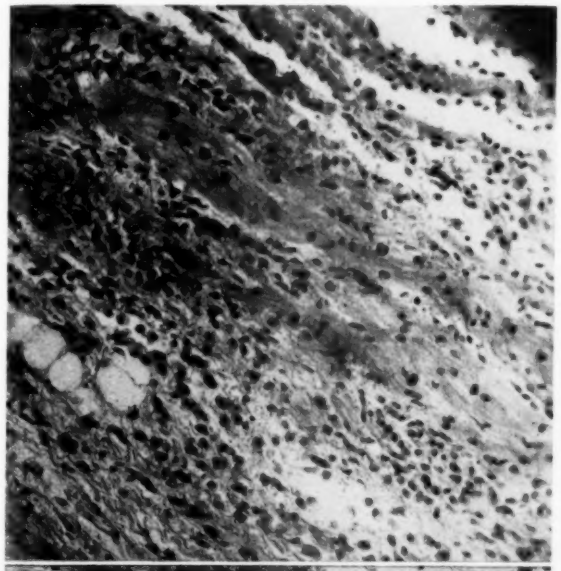

Fig. 5.

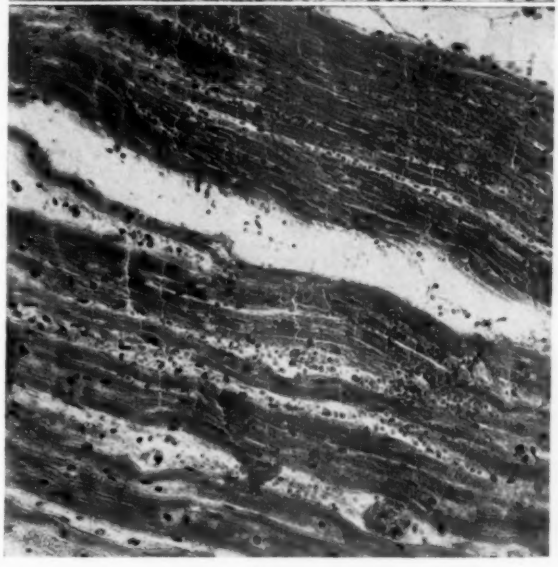

Fig. 4.—Photomicrograph (×340). Iron-hematoxylin and eosin. Section of posterior wall of right atrium showing organizing infarct. There is extensive destruction of muscle fibers and replacement by loose fibrous tissue with numerous fibroblasts and round cells. Note also muscle nuclei showing early degenerative changes.

Fig. 5.—Photomicrograph (×170). Iron-hematoxylin and eosin. Section of posterior wall of left atrium showing recent infarct. There is marked segmentation with early loss of cross striations and cloudy swelling. Note dilation of blood vessels with early hemorrhage.

coronary artery was completely occluded by a reddish-brown, recent thrombus 1.0 cm. from its ostium. The aorta was the seat of moderately late severe arteriosclerosis.

Microscopic Description.— Sections of the myocardium of the posterior wall of the left ventricle and interventricular septum were similar. The myocardium showed considerable changes, with large areas in which the sarcoplasm stained poorly and cross striations were absent. In adjacent areas, the architecture of the myocardial fibers was completely destroyed and obscured by local hemorrhage and exudation of polymorphonuclear leucocytes, many of which showed phagocytic activity. In some sections the infarct showed organization, with new formation of numerous capillaries and young fibrous connective tissue. The pericardial adipose tissue was diffusely infiltrated with polymorphonuclear leucocytes. The epicardium was covered with a loose network of fibrin, enmeshing numerous polymorphonuclear leucocytes.

Sections of the posterior wall of both atria were similar (Figs. 4 and 5). Acute fibrinous pericarditis was also present. In the vicinity of organizing infarction, there were areas in which the myocardial fibers had lost their cross striations and nuclei and had a congealed appearance. Between these fibers there were areas of recent hemorrhage. One section revealed a recent mural thrombus with early organization of the base. Section of the right coronary artery revealed the lumen to be completely occluded by a recent thrombus attached to an intimal plaque.

DISCUSSION

The presence of atrial infarction was correctly anticipated, ante mortem, on the basis of a disturbed auricular mechanism and abnormal contour of the auricular complex in a patient with a typical clinical picture of ventricular myocardial infarction. The coexistence of second and third degree A-V block facilitated the recognition of the displacement of the P-T_A segment. Cushing and associates[1] found abnormalities in the auricular mechanism of the electrocardiogram in 74 per cent of cases of atrial infarction; but in only 9 per cent of all cases of "pure" infarction of the ventricle. These abnormalities included auricular fibrillation, auricular flutter, premature auricular beats, paroxysmal auricular tachycardia, sinus arrest, wandering pacemaker, and A-V nodal rhythm. Similar arrhythmias have followed various types of experimental atrial injury, that is, by cautery, by alcohol injections, and by ligature of atrial arteries.[1,13] Clinically, these arrhythmias are usually transient, but may persist for years.[6,18] Perelman and Miller[6] recently reported the case of a 52-year-old man with myocardial infarction who had multiple disturbances of rhythm and conduction, auricular flutter, fibrillation, and first, second, and third degree A-V block which persisted for three years. Although an autopsy was not performed, the authors felt certain that there was an atrial infarct.

Although there is usually an associated infarction of the ventricle as in our case and in twenty-three of the thirty-one cases of Cushing and associates[1] and in fourteen of Wartman's seventeen cases,[7] atrial infarction may occur alone, or in hearts with hypertrophy or myocarditis.[1] Auricular fibrillation was the most common disturbance of the auricular mechanism in solitary atrial infarction in the series of Cushing and associates.

The posterior location of the atrial infarct and the abnormalities of the contour of the auricular complex are of particular interest in our case. The posterior atrial wall is not commonly involved. Infarction occurred in this location in only three of thirty-one cases.[1] The occurrence of elevation of the

P-R segment (designated as the P-T_A segment by Abramson and associates[14]) in Leads II and III is unusual. We have found no other case reported with similar P-T_A elevation in Leads II and III.

The direction of the P-T_A deviation should depend upon the location of the infarct, in a manner analagous to the S-T deviations in ventricular infarction. Theoretically, injury of the subepicardial myocardium of the posterior basal wall should result in positive deviation of the P-T_A segment in Lead III, usually in Lead II, with negative displacement in Lead I. When the location is anterior or anterolateral, one would anticipate depression of P-T_A in Lead III and elevation in Lead I.[19,20] Such P-T_A depression occurred in Leads II and III in infarction of the right atrial appendage in the cases of Cushing and associates[1] and of Langendorf.[5] Anatomically, the right atrial appendage lies in an anterior or anterolateral position. The high incidence of right atrial appendage infarction as compared with the left atrial involvement has been emphasized. Hence, the rarity of P-T_A elevation in Leads II and III is due to the uncommon involvement of the posterior wall of the atria. In cases of uremia with diffuse fibrinous pericarditis, displacement of the P-T_A segment has not been noted, although characteristic RS-T and T-wave changes occur when the subepicardial myocardium is involved. It is possible that P-T_A displacement occurs when the atria are involved but is undetected. The occurrence of A-V block, as in our case, facilitates the recognition of such deviation.

The clinical recognition of atrial infarction has practical significance. The immediate consequence of atrial involvement is mainly that of a disturbed rhythm, which may precipitate congestive failure if an already damaged heart is subjected to prolonged rapid action. The immediate control of such arrhythmias, if possible, is mandatory.

The subsequent sequelae of atrial infarction include mural thrombosis with thromboembolism, and rupture. Mural thrombi were found adherent to the endocardium over the area of infarction in 84 per cent of the cases of atrial infarction. A similar incidence was noted by Wartman and Hellerstein[7] of which twenty-four per cent showed pulmonary embolism and infarction. The use of anticoagulants would therefore appear logical in atrial infarction, in view of the favorable reports on the value of anticoagulant therapy in the prevention of mural thrombosis and thromboembolism in ventricular infarction.[15-17]

SUMMARY

A case of atrial infarction in a 61-year-old man is presented in which the correct ante-mortem diagnosis was made. Serial electrocardiograms showed a changing auricular mechanism with coarse auricular fibrillation, varying degrees of A-V block, and elevation of the P-T_A (P-R) segment in Leads II and III.

The clinical recognition of atrial infarction, which is more common than generally believed, is important because of the complications of arrhythmias, mural thrombosis, thromboembolism, and rupture.

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SEPTAL INFARCTION WITH COMPLETE HEART BLOCK AND INTERMITTENT ANOMALOUS ATRIOVENTRICULAR EXCITATION (WOLFF-PARKINSON-WHITE SYNDROME): HISTOLOGIC DEMONSTRATION OF A RIGHT LATERAL BUNDLE

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THE most widely accepted explanation of the syndrome of anomalous atrioventricular excitation, and most particularly of the Wolff-Parkinson-White syndrome, is the presence, in addition to the atrioventricular bundle of His, of a functioning anatomic bridge of cardiac muscle from atrium to ventricle of the type described by Kent.[1-5] The existence of such anomalous bundles is said to be uncommon in childhood, rare in adults.[6,7] Structures of this type have been found* on careful serial microscopic examination of the atrioventricular groove in patients with the syndrome. The impulse is apparently conducted over the anomalous bundle sooner than over the atrioventricular bundle, and the activation of the ventricle is eccentric, producing in the typical Wolff-Parkinson-White syndrome a short P-R interval with prolongation of the QRS complex. The difficulty of diagnosing myocardial infarction in such patients[10] has been pointed out,[11,12] and the possibility of making this diagnosis on other than clinical grounds has even been denied.[13] Zoll and Sacks,[14] however, have reported a patient with myocardial infarction whose electrocardiograms showed, in addition to short P-R and prolonged QRS complex, typical coving and inversion of T_2 and T_3. The patient recovered. In view of this patient's history of frequent attacks of paroxysmal tachycardia, these authors considered that the anomaly probably antedated the attack of myocardial infarction. In the case which we are reporting, a clinical diagnosis of septal infarction with intermittent anomalous conduction was made, and post-mortem examination showed massive myocardial infarction involving the septum and the posterior portion of the left ventricle. Further studies revealed the presence of a right lateral bundle.

CASE HISTORY

Mrs. G. V., a 62-year-old widow, was admitted to the Peter Bent Brigham Hospital on June 22, 1947, because of precordial aching, nausea, and vomiting beginning eighteen hours before admission, and coma beginning five hours before admission. The history was obtained from the

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*Because the complete serial examination of the atrioventricular groove in even a single case is so laborious and time-consuming, the number of such studies reported is quite limited. Study of a much larger group of normal hearts is desirable to evaluate the significance of accessory bundles in cases of short P-R interval with prolonged QRS complex.

patient's daughter who had lived away from the patient for a number of years and was uncertain of the details of her mother's health. The patient had, so far as her daughter knew, always been in good health with no complaints or difficulties prior to the present illness.

Physical examination on admission showed an obese, flaccid, unresponsive woman in coma, whose respirations were deep and stertorous. The maximum impulse of the cardiac apex could not be felt. The left border of cardiac dullness appeared to be in the left mid-clavicular line. Being almost synchronous with respiration, the heart sounds were very difficult to hear. The blood pressure, which could be recorded only by the method of palpation, was 60 mm. Hg, systolic. The radial pulse rate was 52 beats to the minute. The lungs were clear, and there was no evidence of congestive heart failure. Neurological examination showed evidence of focal disturbance in the central nervous system, the details of which are not germane to this discussion.

Electrocardiographic examination was carried out shortly after admission. For the most part, the tracings (Fig. 1) showed complete atrioventricular heart block, the atrial rate being 103, and the ventricular, 52 beats to the minute. This rhythm was noted in all but the third complex in Lead I, in the first three complexes in Lead II, and in the last three in Lead III. The ventricular complex during the periods of complete heart block lasted 0.14 second and conformed either to a right bundle branch block or to an idioventricular rhythm with the pacemaker below and to the left of the common atrioventricular bundle. The heart was in the horizontal electrical position. The conventional leads showed a depression of S-T_1, elevation of S-T_2 and S-T_3, and late inversion of T_2 and T_3 of the coronary type. Unipolar limb leads showed a depressed S-T in Lead aV_L, deep Q, elevated RS-T, and late inversion of T in Lead aV_F. Unipolar chest leads during the period of complete block showed late intrinsic deflection in Leads V_1 through V_4, early intrinsic deflections in Leads V_5 and V_6, deep Q in Leads V_1 through V_3, and deep Q, elevated RS-T, and late inversion of T in Lead V_4. The last three complexes in Lead II and the first three in Lead III, on the other hand, showed atrioventricular conduction with short P-R interval (0.10 to 0.12 second), increased QRS duration (0.14 second), no Q waves, but the same late inversion of the T waves. This indicates that the ventricles were invaded by the electrical impulse in different ways, depending upon whether the impulse was or was not conducted from the atrium, but that electrical regression was the same in either case. The P waves, whether or not conducted, were low, almost isoelectric, notched, and prolonged in Leads II and III. Isolated beats showing short P-R intervals and a different form of ventricular complex were also recorded in Lead I (third complex), in Lead aV_R (first complex), in Lead aV_F (second complex), in Lead V_2 (second complex), and in Lead V_3 (second complex), these conducted impulses breaking up the slow idioventricular rhythm. The atrial and ventricular rates during the period of atrioventricular conduction were 55 beats to the minute.

Other routine laboratory examinations were not remarkable. The patient failed to rally, remained comatose, became cyanotic, and died five hours after admission.

Post-mortem Examination.—At autopsy the entire interventricular septum and posterior portion of the left ventricle near the apex were infarcted. The myocardium in these infarcted areas was soft and spongy and dark greyish-yellow centrally. About the periphery of the infarct numerous petechiae were seen. Other gross findings were cardiac enlargement (420 grams), mural thrombus along the interventricular septum in the left ventricle, normal heart valves, and marked arteriosclerotic narrowing of the coronary arteries without fresh thrombosis.

Microscopic examination showed extensive fresh infarction of the myocardium in the regions of infarction described grossly. This is illustrated in Fig. 2 which is a transverse section taken across the interventricular septum just beneath the "undefended space" of the heart, which is the area through which the atrioventricular bundle passes. Scattered throughout all sections were small areas of fibrosis regarded as evidence of long-standing coronary insufficiency.

Serial microscopic sections were also taken of a block of tissue from the right posterolateral aspect of the heart along the atrioventricular groove including 1.9 cm. of atrial and ventricular muscle on each side of the groove. Every fifth section was stained with Masson's trichrome stain. These sections (Figs. 3 and 4) showed a band of healthy cardiac muscle bridging the fibrous and fatty tissue of the atrioventricular groove (Fig. 3) continuous with the ventricular muscle (Fig. 4). Technical difficulties prevent us from reproducing a complete connection between the bundle and

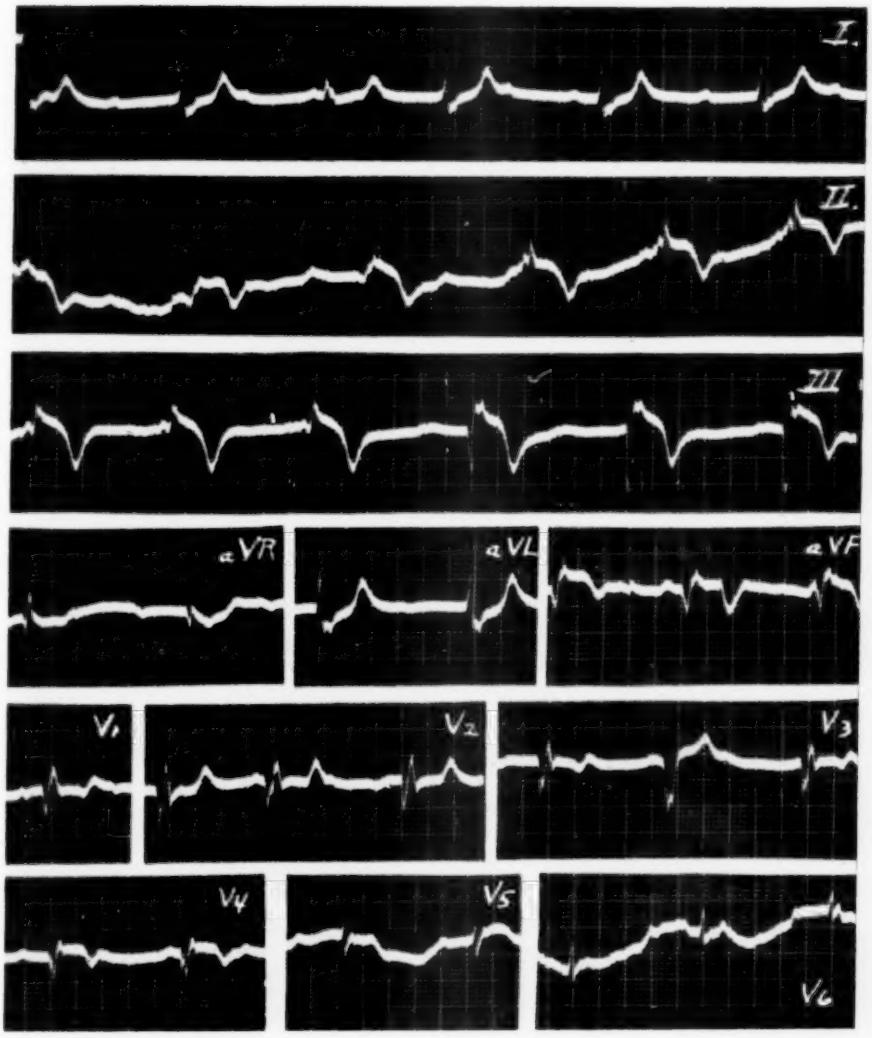

Fig. 1.—Twelve lead electrocardiograms showing complete heart block with a ventricular rate of 52 and an auricular rate of 103. Heart in horizontal electrical position. S-T_1 is depressed and S-T_2 and S-T_3 are elevated. There is late inversion of T_2 and T_5 with coronary contour. The first three complexes in Lead III show atrioventricular conduction, but the P-R interval is only 0.10 second. The deep Q shown in the following three dissociated ventricular complexes is not present in these conducted impulses, indicating a different method of invasion of the ventricle by the impulse. The heart rate during atrioventricular conduction is 55 per minute. Isolated beats showing atrioventricular conduction with short P-R interval are seen in Leads I, aV_R, aV_F, V_2, and V_3 where they interfere with the slow idioventricular rhythm. The QRS interval during block and during atrioventricular conduction was 0.14 second. The intrinsic deflection is late in Leads V_1 through V_4, early in Leads V_5 and V_6. Thus, either right bundle branch block is present or there is an idioventricular rhythm with a pacemaker below and on the left ventricular side of the common atrioventricular bundle. Q waves are present in Leads V_1 through V_6. These tracings were regarded as characteristic of posterior myocardial infarction. The complete heart block and the possible right bundle branch block were regarded as very suggestive of septal infarction and the periods of rapid atrioventricular conduction of the presence of a functioning collateral atrioventricular bundle.

the auricular muscle, but the nature of the bundle and its deep penetration into the auricular tissue leave no doubt of their continuity.* Further studies of the atrioventricular groove to demonstrate the possible presence of additional muscular connections between the atria and ventricles were not undertaken.

Fig. 2.—Hematoxylin-eosin section of basalar portion of interventricular septum (×45) with fibrous "undefended space" just above and to the right. Extensive fresh infarction of myocardium in region through which atrioventricular bundle (His) courses, a pathological basis for complete heart block.

DISCUSSION

This case is remarkable in many respects. (1) A clinical diagnosis of myocardial infarction was made in the face of anomalous conduction and was confirmed at post-mortem examination. The available literature contains no reference to a similar case. (2) An accessory bundle was suspected from the electrocardiographic pattern and found on careful microscopic examination of the atrioventricular groove. (3) Involvement of the interventricular septum, and particularly of its upper portion, the site of the atrioventricular bundle, was postulated from the presence of complete heart block and confirmed at necropsy. (4) Experience[15-19] has shown that certain pharmacologic agents (atropine, digitalis, quinidine, epinephrin) or physiologic procedures (exercise, change in position, carotid sinus pressure) can cause the impulse to be conducted down the path of least resistance, be it the atrioventricular or the anomalous bundle. In the present case a pathologic process, myocardial infarction, produced com-

*This is not only the conclusion of the authors, but also the conclusion of pathologists whose opinion was sought. We regret that in cutting the sections several important ones were lost.

Fig. 3.

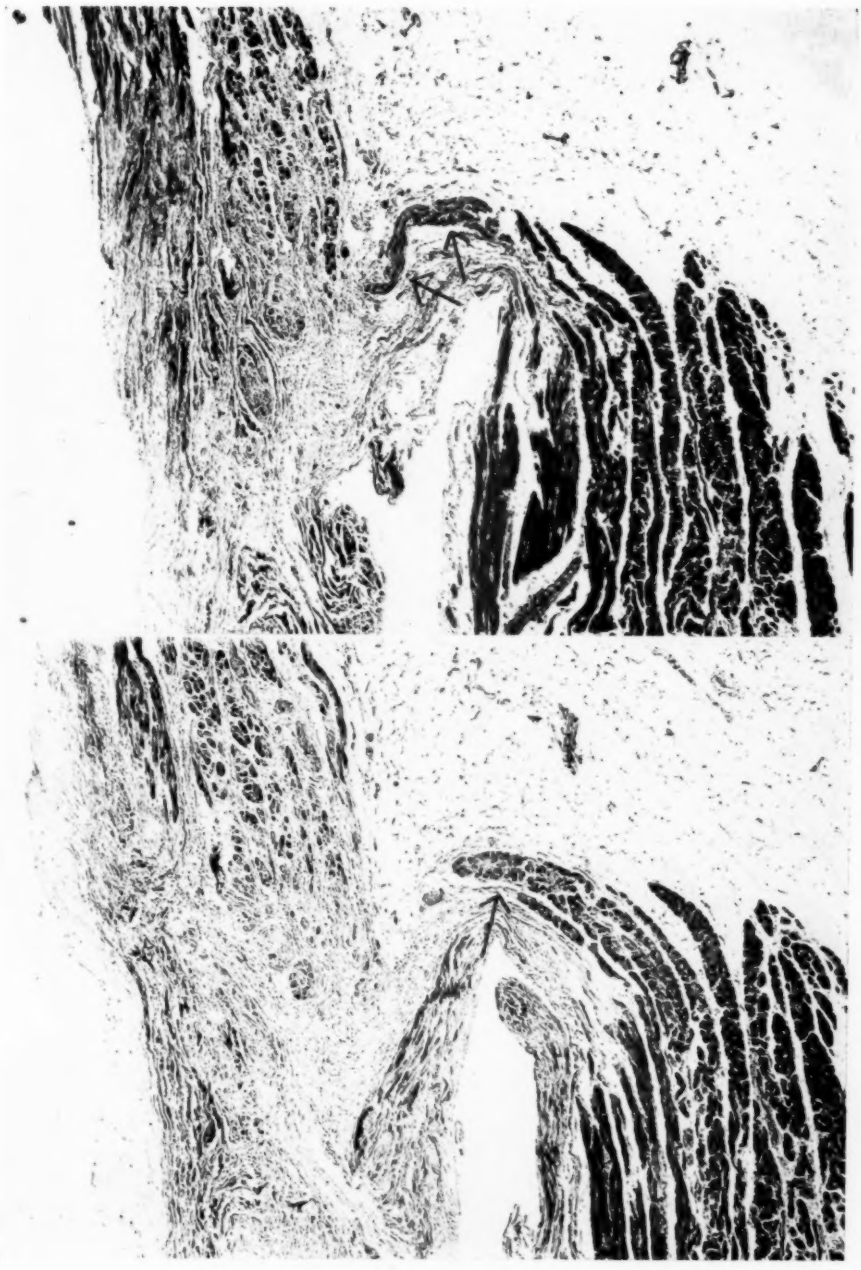

Fig. 4.

Fig. 3.—Section from right posterolateral aspect of atrioventricular groove. Masson's trichrome stain (×45). Bridge of healthy cardiac muscle extending across fibroareolar tissue of atrioventricular groove, an anatomical basis for aberrant atrioventricular conduction. Muscle of right auricle at upper left, of right ventricle at lower right. Tricuspid valve, lower left.

Fig. 4.—Same, thirty-five sections beyond section shown in Fig. 3, demonstrating continuity of bridge with ventricular muscle.

plete block in the normal atrioventricular bundle so that the ventricles either beat at their own inherent rate or were activated by impulses traversing the healthy anomalous bundle. This represents a nice anatomical-physiological correlation and is quite consistent with the hypothesis of an aberrant pathway as the explanation for the syndrome of short P-R interval with prolonged QRS complex.

The location of the anomalous bundle (Figs. 3 and 4) in the present case corresponds to that described in the anatomical studies of Kent[5] and to the physiological studies of Rosenbaum and associates[18] in that ventricular activation must proceed from the subepicardial to the subendocardial layers of the heart rather than in the normal subendocardial to subepicardial direction.

In this case the RS-T segment deviation and the coronary type of T-wave inversion were present during both normal (or relatively normal) and anomalous ventricular excitation, whereas the QRS changes (small Q_2, deep Q_3) were noted only during normal excitation. It seems, then, that in the syndrome of short P-R interval, prolonged QRS complex with posterior myocardial infarction, the change in the initial ventricular complex may be obliterated when the ventricles are stimulated via the anomalous pathway but the changes in the final deflection persist.* Thus, the diagnosis of posterior myocardial infarction in the presence of constant anomalous conduction[14] must depend upon changes in the RS-T segment and in the T wave. If, however, some of the impulses pursue normal or relatively normal pathways, QRS changes may be noted as well.

SUMMARY

A proved case of myocardial infarction involving the interventricular septum showed complete heart block and intermittent anomalous atrioventricular excitation (short P-R interval, prolonged QRS complex). At necropsy an accessory right lateral bundle was found bridging the atrioventricular groove at the right posterolateral aspect of the heart. In this case anomalous ventricular excitation obliterated the QRS changes of posterior myocardial infarction, but the RS-T and T-wave changes persisted.

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*When the free wall of the ventricle (septal activation being neglected) is activated from the endocardial to the epicardial surface, a deep downward deflection (Q wave) is recorded in the ventricular cavity; an electrode overlying a transmural infarct of this free wall, therefore, records a Q wave. On the other hand, when the free wall of the ventricle is activated from the epicardial to the endocardial surface, an initial upward deflection is recorded in the ventricular cavity; therefore, an electrode overlying a transmural infarct of the free wall no longer records a Q wave.

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Clinical Reports

CONGENITAL TRICUSPID ATRESIA ASSOCIATED WITH INTER-AURICULAR AND INTERVENTRICULAR SEPTAL DEFECTS

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RECENT advances in cardiac surgery offer hope that more can be done for cases of congenital heart disease. This presupposes accurate clinical recognition of the various complexes. The following case is an example of one of the rarer anomalies, but the picture is typical and it is hoped that this report will help others to recognize this congenital malformation during life.

CASE REPORT

M. B., a white female child, was cyanotic at birth and had moderate respiratory difficulty. An apical systolic murmur and precordial systolic thrill led to the diagnosis of congenital heart disease, but the cyanosis cleared up within a few days and did not reappear until several months later.

She was readmitted to the hospital at the age of 4 months because of a persistent upper respiratory infection and frequent vomiting. At home she had been vomiting occasionally for about four weeks, but she was well nourished and her weight was normal. With the onset of the recent acute symptoms, the mother had noted persistent mild cyanosis. The temperature on admission was 102° F., and roentgenogram of the chest showed bronchopneumonia. She responded to treatment and was discharged, but after this episode the dyspnea and cyanosis were persistent and increasingly severe, requiring frequent administration of oxygen.

At the age of 3 years, 4 months, the child developed an acute tonsillitis and otitis media. She was treated at home with sulfadiazine and penicillin and seemed to be improving, but several generalized convulsions caused her to be readmitted to the hospital. She seemed acutely ill and had a temperature of 101° Fahrenheit. Physical examination showed extreme cyanosis, clubbing of the fingers and toes, and moderately injected eardrums. The heart was enlarged and there was a strong precordial pulse and thrill. There was a systolic murmur, loud and machinelike in character, and a faint presystolic murmur, both maximal in the third intercostal space at the left sternal border. A high-pitched systolic murmur of a different character was heard best in the pulmonic area. The pulse was regular and rapid. The electrocardiogram showed left axis deviation. An x-ray film of the chest (Fig. 1) showed left ventricular hypertrophy.

The urine was negative except for many white blood cells in the sediment. A urine culture showed *Staphylococcus albus*. The red blood cell count was 5,900,000 per cubic millimeter, the white blood cell count was 13,500 per cubic millimeter, and the differential showed 85 per cent

From the Marshfield Clinic and St. Joseph's Hospital.
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segmented polymorphonuclear leucocytes, 13 per cent lymphocytes, and 2 per cent mononuclear cells. The sedimentation rate was 6 mm. in one hour.

In spite of the administration of sulfadiazine and penicillin, the temperature remained elevated. Soon there appeared an outward deviation of the right eye and weakness of the left

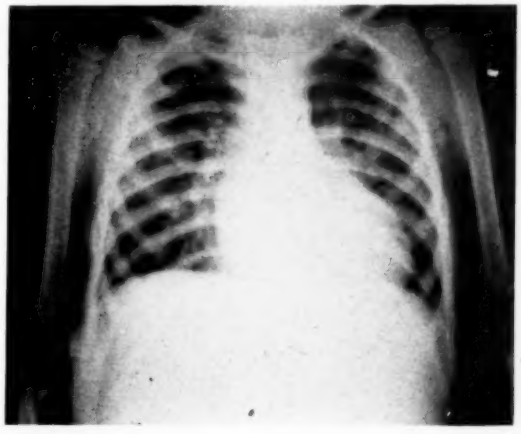

Fig. 1.—Roentgenogram of the chest showing the typical cardiac silhouette. Note the absence of the shadow normally cast by the pulmonary conus.

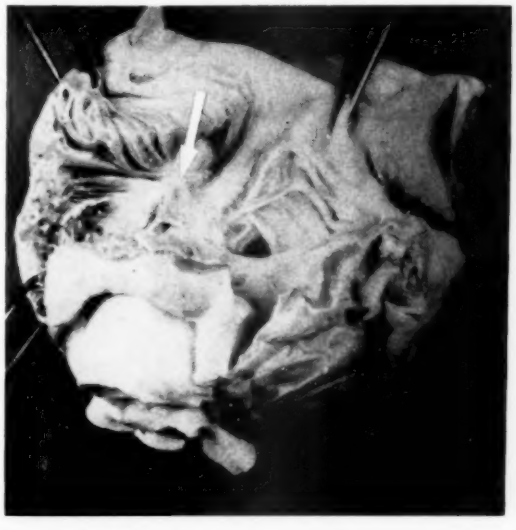

Fig. 2.—Looking down into the right auricle. The arrow points to the atresic tricuspid orifice. Below is the interauricular septal defect.

arm and leg. Examination revealed positive Babinski and Chaddock signs bilaterally, hyperactive deep reflexes, a left pupil which was larger than the right, and bilateral choking of the optic discs. The presumptive diagnosis of subacute bacterial endocarditis with cerebral embolism and abscess formation was made, but numerous blood cultures failed to reveal the expected bacteremia. The white blood cell count rose steadily to 50,000 cells per cubic millimeter, as did

the fever, which terminally measured 106° Fahrenheit. In spite of intensified penicillin therapy, the child became comatose and died following the onset of cardiac decompensation.

Necropsy.—A complete necropsy was performed, but only the main lesions will be reported. Aside from generalized congestion of the viscera, cyanosis of mucous membranes, and clubbing of the fingers and toes, the findings of interest are limited to the heart and brain.

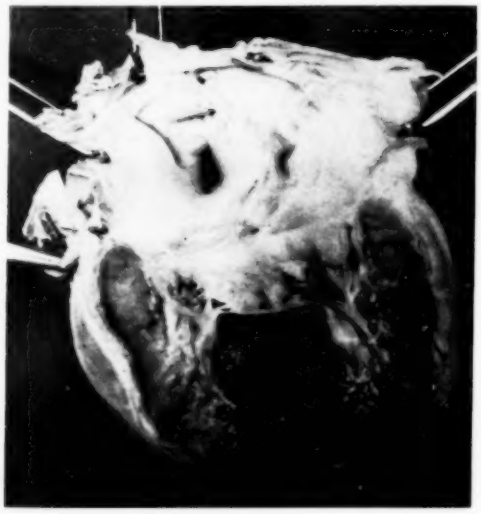

Fig. 3.—Left auricular aspect showing the interauricular septal defect and the hypertrophied left ventricle.

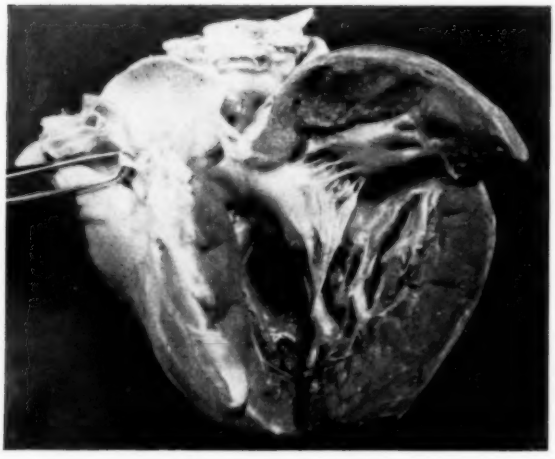

Fig. 4.—Showing the interventricular septal defect.

Heart (Figs. 2, 3, and 4): The weight was 120 grams (normal weight, about 70 grams). The epicardium was smooth and glistening. The epicardial fat was normal. The preponderance of weight was on the left side, which was very firm. The right auricle showed the endocardial surface to have many fibrous trabeculae. When opened it appeared larger than normal, measuring 8.0 cm. in circumference. Where the tricuspid orifice should have been, there was only a

depressed fibrous dimple. There was an interauricular septal defect measuring 2.0 by 1.0 centimeter. The right ventricle, which was not directly connected with the right auricle, was very small, although the wall was thick (8.0 mm.). The pulmonary leaflets were more fibrous than normal, the pulmonary ring measured 3.5 cm. in diameter, and the pulmonary artery was normal. The ductus arteriosus was closed. The left auricle was large, measuring 8.0 cm. in diameter. The mitral valve was normal and measured 7.5 centimeters. The left ventricular wall measured 14 mm. in thickness. Behind the mitral valve, there was an interventricular septal defect measuring 1.5 by 1.0 centimeter. The aortic valve was normal, and the aortic ring measured 3.5 centimeters. The root of the aorta was normal. The coronary arteries were normal.

Brain: The dura was normal. When the brain was exposed, the right hemisphere was found to be soft and fluctuant, as was the occipital lobe of the left hemisphere. Coronal sections showed a large abscess, 4.0 by 5.0 by 5.0 cm. in the frontal lobe on the right, and a similar abscess in the occipital lobe on the left. There was much exudate over the pia-arachnoid on both sides.

Middle Ear: The middle ear on the right contained creamy pus. The left was normal.

Final Anatomic Diagnosis: Congenital tricuspid atresia; septum primum with ostium atrioventriculare commune; interventricular septal defect; chronic otitis media, right side; brain abscesses, multiple.

DISCUSSION

This case illustrated accurately both the clinical and anatomic findings. Clinically the picture is clear and, in retrospect, not to be confused with that of other congenital anomalies. In the cyanotic group this is the only lesion which gives a left axis deviation of the electrocardiogram and is thereby easily distinguished from cases of tetrology of Fallot. Furthermore, the roentgenogram of the cardiac silhouette is characteristic in that there is an absence of the convexity normally cast by the pulmonary conus, and a slight concavity in this region is usual (Fig. 1). These two findings should enable one to make a diagnosis regardless of the murmur present.

As a matter of fact, murmurs are not diagnostic in this syndrome, many varieties having been described in the reported cases. It is easy to see that the abnormal intracardiac course of the blood depends on the associated lesions, and particularly on the relative size of the interauricular and the interventricular defects. In one case[14] no murmurs were present in spite of extreme anatomic defects.

Anatomically this case is typical of the majority of cases reported. Although various associated abnormalities are reported, the simplest and most common is illustrated by the defects in the interauricular and interventricular septum; such defects are necessary to surmount the atresia of the tricuspid valve. In the absence of a patent ductus, the interventricular defect is of course necessary.

Although it is said that fetal endocarditis is sometimes the cause of the atresia, histologic sections through the atretic area failed to show any signs of inflammatory disease. The mechanical explanation is more likely. If the endocardial cushions, which are the anlage of the valve leaflets, hypertrophy and fuse so as to shut off the normal valve opening, the blood flow would prevent the closure of the ostium primum, and, similarly, there would be a failure of the interventricular ostium to close. Since in the complex here described there was no transposition of the vessels, the atresia can be assumed to have occurred

before the eighth week, when the septa closed, and after the obliteration of the right-sided aorta.

Tricuspid atresia is relatively rare. In Abbott's[1] series of 1,000 cases, twenty-five instances of tricuspid atresia are listed. We have been able to find reports of an additional fifteen cases.[2-15]

SUMMARY

1. A case of congenital tricuspid atresia with associated defects is presented.

2. The clinical picture is typical and easily distinguishes this condition from other congenital malformations in the cyanotic group.

3. This is the forty-first reported case.

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GANGRENE OF LOWER EXTREMITIES IN INFANTS

Report of Two Cases

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ARTERIAL occlusion with gangrene of extremities is commonly encountered in adults and is usually due either to embolism or disease of the vessel wall. Gangrene of extremities in infants, however, is very rare. In 1945, Gross[1] reported six cases of his own and reviewed forty-one other reported cases. A similar review was made in 1941 by Heller and Alvari.[2] Von Khautz,[3] in 1914, reported a group of fifty cases of gangrene in children varying in age from newborn to 15 years of age. Of these fifty cases, thirty-nine occurred after or during acute infections such as diphtheria, typhoid, scarlet fever, pneumonia, and so forth. Of the fifty cases reported in this series, twenty-one recovered, sixteen died, and the outcome of thirteen cases was not known. Because of the rarity of gangrene in infants we feel that the report of two cases, with necropsy findings in one case, may be of interest.

CASE REPORTS

Case 1.—M. H., a 3½-month-old white boy, was admitted to the Coney Island Hospital on Nov. 3, 1946, with a history of fever beginning on the sixth day of life and followed by diarrhea and vomiting. The family history revealed that two other male children previously had suffered from a similar condition, consisting of fever of unknown origin and diarrhea.

On admission the child was vomiting and had severe diarrhea. Physical findings were essentially negative. While the infant was in the hospital the temperature was elevated most of the time, ranging from 100° to 108° F.; on occasional days the temperature was normal.

X-ray examination of chest and abdomen, urine examination, and blood studies were negative. Blood count revealed hemoglobin, 13 grams; red blood cells, 4,830,000; white blood cells, 4,800, with 40 per cent polymorphonuclear leucocytes, 45 per cent lymphocytes, and 15 per cent monocytes. Basophilic stippling was present. The platelets were normal. Treatment consisted of several transfusions, change of feeding formula, and penicillin, without any apparent improvement.

On the sixteenth hospital day evidence of disturbed circulation in the lower extremities appeared. There was a patchy cyanosis and edema of the right leg and foot extending to a level slightly below the knee. There were several areas of necrosis of the left leg and foot involving the areas where incisions were made for transfusions and where bone marrow transfusion in the left tibia had been given. There were several areas of necrosis and ecchymosis on the left thigh and gluteal region where penicillin was injected. Both feet and legs were cold to touch, the right

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being colder. Pulsations of both femoral arteries were normal but pulsations of both the dorsalis pedis and posterior tibial arteries were absent. Oscillometric readings made on both thighs were absent. Heparin was given intravenously, after which the color and temperature of the right leg and foot improved except for dry gangrene of the first three toes. The necrotic areas on the left lower extremity were unaffected. The patient died on Nov. 27, 1946. The final clinical diagnosis was, "Fever of unknown origin and thrombosis of both femoral arteries." Autopsy was not obtained.

CASE 2.—A. M., a 2-year-old white girl, was admitted to the Coney Island Hospital because of temperature, cough, and difficult breathing. Examination on admission revealed a pale, acutely ill, mentally and physically retarded baby. Coarse râles were scattered throughout both lung fields. There was no dullness present. The pharynx was mildly inflamed. The diagnosis was asthmatic bronchitis with bronchopneumonia and mongolism. During the hospital stay the temperature ranged from 100° to 107° F., and an intermittent watery stool developed on the

Fig. 1.—Section of artery (× 26) and adjacent veins. Recanalization of thrombus in the artery is noted.

sixth hospital day. The patient was given penicillin and adrenal cortex therapy. On the seventh hospital day cyanosis of the right foot and the large and middle toes developed with a decrease in skin temperature and blanching below the knee. The cyanosis spread to the other toes and remained so throughout hospitalization. Both feet were cold to touch, the right being colder than the left. Pulsation of the left femoral artery was normal, and the right femoral was questionable. Oscillometric readings were absent in both thighs and ankles. The average skin temperature of the toes of the right foot was 78° F. and of the left foot varied between 80° and 83° Fahrenheit.

X-ray films revealed an anomaly of the skull and pneumonia of the right upper lobe. Serum calcium was 10 mg. per cent; phosphorous, 4.0 mg. per cent; cholesterol, 266 mg. per cent; cholesterol esters, 143 mg. per cent; thymol gel, 2; hemoglobin, 10.5 Gm.; red blood cells, 4,270,000; white blood cells, 9,600, with 68 per cent polymorphonuclear leucocytes, 30 per cent lymphocytes, and 2 per cent monocytes.

The patient expired on the ninth hospital day.

Necropsy.—The post-mortem examination revealed a mottling of the skin of the right foot There was also a mottled bluish discoloration of the left lower leg extending from the ankle to the mid-calf. The right big toe was blue-black in color and the skin was dry and friable. There was evidence of consolidation of the lower lobes of both lungs. The liver showed moderate congestion. The rest of the organs were examined and found to be grossly normal. The right iliac and femoral arteries and veins were smooth walled; the right posterior tibial and dorsalis pedis arteries showed firmly adherent thrombi which completely occluded the lumina of these vessels.

Fig. 2.—Section of arterial thrombus (× 110).

Sections of vessels from the right leg and foot (Figs. 1 and 2) showed a medium-size muscular type of artery whose lumen was filled with fibrin, with marginated clumps of erythroyctes and nucleated blood cells. The fibrin strands were poorly defined. At the periphery there were spaces partly lined by endothelium and filled with erythrocytes. Adjacent to one such vessel was a pair of intact smaller caliber veins. Other sections of arteries from this area showed similar thrombosis and recanalization. One small vein showed an unorganized thrombus. There was no inflammatory reaction in or about the walls of these vessels.

Sections of the skin of the right big toe showed poor histologic detail. There was vesiculation of the epidermis. There was marked subcutaneous edema and the capillaries were engorged. The collagenous fibers were poorly defined. No inflammatory reaction was present.

The lungs revealed changes typical of bronchopneumonia. The spleen revealed diffuse lymphoid hyperplasia and marked congestion of sinusoids. The kidneys showed congestion of renal vessels and moderate hyalin degeneration of tubular cells. Heart muscle presented moderate interstitial edema. Liver revealed slight congestion of hepatic capillaries. The rest of the organs were of average structure.

DISCUSSION

Infection and toxemia were present in both of these cases. In the first, these were of unknown origin; the second case had extensive bronchopneumonia. Severe diarrhea was present in both infants and vomiting resulting in dehydration in one.

The pathologic findings in the second case revealed a bland thrombus in the right dorsalis pedis and posterior tibial arteries without any involvement of the vessel walls. There was also thrombosis of a small vein. There was no abnormality of the heart and no evidence of any sources of emboli. The presumptive cause of thrombosis and gangrene in each of the two infants was infection.

It is well established that arterial and venous thrombosis may develop in vessels which are adjacent to a localized infection. This is explained by the fact that the infecting organisms produce local trauma to the intima of the vessel, platelets adhere to that area, thromboplastin is produced, and a clot forms. In these two cases the thrombosis may well be explained on the basis of changes in the blood which are brought about by the infection in the body. These changes include: (1) Increased viscosity of the blood produced by rise in temperature, marked sweating, vomiting, and diarrhea, all of which produce dehydration. (2) Increase in fibrinogen and changes in the electrolytes. (3) Increase in adhesiveness of the blood platelets and increased coagulability of blood plasma. Not all of these factors may be present in the same case, but any one of these may induce thrombosis.

SUMMARY

1. Two cases of gangrene of the extremities in infants, due to arterial thrombosis following systemic infection, are presented.

2. In the absence of arterial disease and a focus for embolization, it is presumed that the thromboses were caused by factors which increased the coagulability of blood.

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RECURRENT SPONTANEOUS MEDIASTINAL EMPHYSEMA SIMULATING MYOCARDIAL INFARCTION

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RECOGNITION that mediastinal emphysema may occur spontaneously, unattended by infection or trauma, has its origin in the papers of Hamman,[1] the first of which appeared in 1934. Since that time a total of forty cases have been reported in the medical literature.[2,3] Modern concepts of the pathogenesis of mediastinal emphysema have as their earliest basis the writings of Müller (1888), but it is Macklin[4,5] to whom we are indebted for clarifying and expanding our knowledge of this disease by demonstrating experimentally the manner of its occurrence, namely by dissection of air into the perivascular connective tissue of the pulmonary blood vessels to the hilus and mediastinum.

Clinically the syndrome is characterized by pain of sudden onset which is usually substernal or precordial in location. The pain varies in intensity from a vague discomfort or soreness to a severe oppression. It commonly radiates to the left shoulder and down the left arm, or up into the neck. Dyspnea, if present, is usually mild. The patient is often aware of a crackling or gurgling sensation in his chest. Fagin and Schwab[3] emphasize the absence of the picture of shock, hypotension, or appreciable tachycardia in all previously reported cases.

The first suggestive physical sign, when present, is a peculiar crunching, crackling sound (Hamman's sign) heard over the precordium during both phases of the cardiac cycle on auscultation of the chest. The area of cardiac dullness may be diminished or obliterated by a hyperresonant note on percussion. There may be a coexisting pneumothorax. Significant change in pulse, temperature, or blood pressure is uncommon. Appreciable leucocytosis, elevation of the sedimentation rate, or alteration of the electrocardiogram is absent. The roentgenogram may or may not reveal the presence of air in the mediastinum.

The following case is of interest because of the associated signs of shock and marked hypotension which were absent in all previously reported cases of this syndrome. The emphysema in this case was recurrent, and roentgenographic evidence of air in the mediastinum was present during the second episode.

REPORT OF A CASE

The patient, a 23-year-old Army Air Force pilot, was admitted to the Medical Service of the Wright Field Station Hospital on March 10, 1947, in transfer from the Dispensary at Wilmington (Ohio) Air Base, with a complaint of weakness.

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Family history revealed that the patient's father, 72 years of age, was said to have a "weak heart"; and a sister, 32 years of age, was invalided by rheumatic heart disease.

A review of past medical history revealed only scarlet fever in childhood without complications or apparent sequelae.

Present Illness.—At about 10 o'clock in the evening, three days prior to admission to the hospital, the patient became aware of the gradual onset of a sensation of "pressure" over the anterior part of the chest which he attributed to indigestion. Earlier in the evening the patient had had two glasses of beer and two mixed drinks. The sense of oppression gradually became more intense until it definitely established itself as actual pain which, as it reached its maximum severity, radiated to the left shoulder and down the left arm. The patient became dizzy and nauseated and broke out in a profuse perspiration. He experienced a profound sense of weakness and had to be carried bodily to the car which was to take him from town to the base dispensary. His companions described him as cold, clammy, and apathetic, though apparently in acute pain. He reached the dispensary at 5 A.M. and was seen by the base medical officer who found the patient in a state of shock. The skin was ashen gray, cold, and clammy. He responded feebly when spoken to. The pulse was weak and irregular, the rate 125 per minute. The blood pressure was 80/50. The heart sounds were slapping in character, and on auscultation of the precordium a crunching, crackling sound was heard during systole and diastole. This was interpreted at the time as a friction rub. The patient was presumed to have suffered an acute myocardial infarction and was given a hypodermic of ½ grain of morphine and 1/200 grain of atropine sulfate. This was repeated every four hours during the following twenty-four hours. Oxygen, by mask, was administered. The blood pressure was recorded every fifteen minutes and rose in two hours from 80/50 to 90/60. The patient could not recall how he felt in the twenty-four hour period following admission to the dispensary because he was heavily narcotized, but on the second day following the onset of his illness he was free of pain, required no analgesics, and complained only of a feeling of weakness. The following morning he was transferred to the Station Hospital, Wright Field, Ohio.

On admission to the hospital, on March 10, 1947, the patient did not appear ill. Aside from slight weakness he was asymptomatic.

Physical Examination.—Temperature on admission was 98.4°F. The pulse rate was 84 per minute and regular. The blood pressure was 100/60. The heart was of normal size and contour. The heart tones were of good quality; there were no murmurs or other adventitious sounds. The lungs were clear. The extremities revealed no calf tenderness or swelling. Homan's sign was negative bilaterally.

An electrocardiogram made on the day of admission revealed a sinus arrhythmia with a rate of 62 per minute. The P-R interval was 0.16 second. There were deep S waves in Lead I; R_2 and R_3 were tall. The RS-T segment of the limb leads was within normal limits. Chest leads CF_2, CF_4, and CF_5 were normal.

The sedimentation rate was 10 mm. in one hour (Wintrobe). Hematocrit was 48. There were 7,500 white blood cells with 62 per cent neutrophiles, 37 per cent lymphocytes, and 1 per cent eosinophiles. Urinalysis was normal. A chest x-ray (posteroanterior view) showed no abnormality.

On March 12, a second electrocardiogram was unchanged from that made on admission. The patient felt well and clamored to be up and around. Following the second electrocardiogram he was permitted to do so. On March 13, the white blood cell count was 7,900 and the sedimentation rate was 8 mm. in one hour. On March 17, a third electrocardiogram was unchanged from those taken previously. During the entire hospitalization the patient was asymptomatic. He was returned to full duty on March 18, 1947.

It was felt that the symptom complex was best explained on the basis of a spontaneous mediastinal emphysema. The nature of the illness was explained to the patient and it was suggested to him that if he should have a recurrence of chest pain, chest x-rays in the posteroanterior, lateral, and oblique views should be taken at his base medical installation.

On March 23, five days after discharge, the patient was readmitted to the hospital. He stated that since discharge he had felt well except for slight vague precordial discomfort. The evening

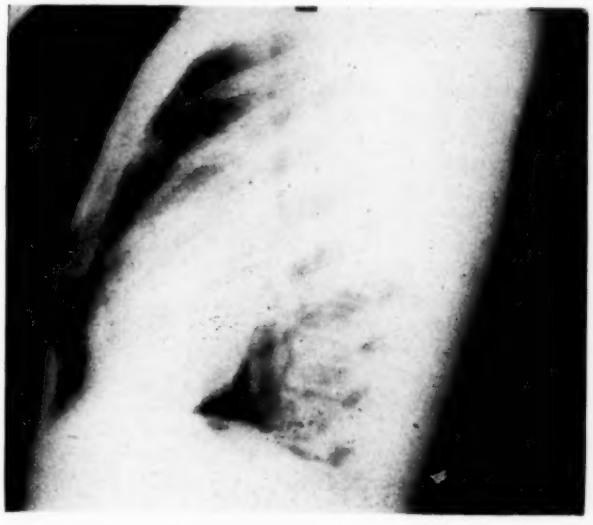

Fig. 1.—Lateral view of chest taken on day of second admission (March 23, 1947) demonstrating area of radioparency anterior to the heart. (Courtesy of Capt. G. L. Hekhuis, Chief of Radiology, Station Hospital, Wright Field.)

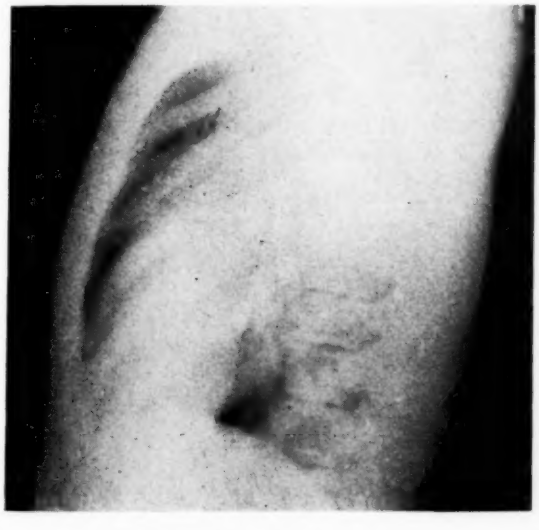

Fig. 2.—Lateral view of chest five days after second admission, illustrating complete return to normal. (Courtesy of Capt. G. L. Hekhuis, Chief of Radiology, Station Hospital, Wright Field.)

before readmission, while sitting quietly playing cards, the patient suddenly experienced sharp precordial pain, continuous in character. The patient stated it was like the pain of the previous episode but less severe. A distinct sense of "gurgling" in the chest was experienced which was aggravated by the prone position and relieved by an upright position. Examination by the base medical officer at that time revealed a crunching sound over the sternum and precordium like that which had been heard during the first episode. Posteroanterior, lateral, and oblique views of the chest were taken.

Examination on admission revealed an adult young man who did not appear ill. Temperature was 98.6° F; pulse, 76 per minute and regular, and blood pressure, 110/60. The area of cardiac dullness over the anterior chest wall was obliterated by a hyperresonant percussion note. A crunching sound over the sternum was audible during the entire cardiac cycle. The patient was aware of "gurgling" in the chest at the time of examination and was able to produce the noise willfully for listeners by assuming a recumbent position. The lungs were clear and the remainder of the physical examination was normal.

Sedimentation rate 4 mm. in one hour. The white blood cells were 6,400 with 49 per cent neutrophiles, 42 per cent lymphocytes, 6 per cent monocytes, and 3 per cent eosinophiles. Urinalysis was negative. An electrocardiogram revealed no change from tracings made on the previous admission. Examination of the x-ray films brought by the patient revealed, in the lateral view, an area of increased radioparency anterior to the heart extending from the mid-portion of the sternum inferiorly to just above the diaphragm. It was not visualized in the other views. X-ray films taken on admission revealed the same finding in the lateral view (Fig. 1).

On March 26, there was marked reduction in the area of radioparency previously visualized. On March 27, re-examination by x-ray showed further reduction. On March 28, there was complete disappearance of the area of increased radioparency previously seen in the lateral view films of the chest (Fig. 2). The last x-ray films were taken on April 2 and were normal in all views.

During the entire course of hospitalization the patient felt well. He had no chest pain; Hamman's sign was no longer audible after the second hospital day.

The patient was discharged on April 3, 1947, to convalescent leave. Blood pressure at the time of discharge was 126/80. The patient was last seen on May 27, 1947. Physical examination was normal. Blood pressure was 130/84. He has remained well since discharge from the hospital.

SUMMARY

1. A case of recurrent spontaneous mediastinal emphysema simulating myocardial infarction in a 23-year-old man is reported.

2. The presence of signs of shock and hypotension, not previously reported in association with this syndrome, are described.

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Abstracts and Reviews

Selected Abstracts

Goodman, M. J.: Periarteritis Nodosa With Recovery; Report of an Unusual Case Apparently Due to Sensitivity to Sulfadiazine. Ann. Int. Med. **28**:181 (Jan.), 1948.

A 17-year-old white boy was admitted to the hospital after he had been treated for an acute upper respiratory infection with two courses of sulfadiazine, following which an erythematous purpuric rash, nose bleeds, fever, and generalized body aches and pains developed. These symptoms were interpreted to be a manifestation of sensitization to the drug. During his hospital stay, he developed hematuria, cylindruria, albuminuria, and a moderately severe degree of hypertension. He was extremely toxic and remained febrile for several weeks. Changes in serial electrocardiograms suggested the presence of an acute myocardial lesion. Eosinophilia in the blood smears was not a striking feature. Biopsy of the deltoid muscle established the diagnosis of periarteritis nodosa. A spontaneous recovery occurred following general supportive therapy. Examination of the patient two years after his discharge from the hospital indicated that he was in splendid health.

WENDKOS.

Rees, C. E.: A Cause for the Reestablishment of Communication Following Ligation of Patent Ductus Arteriosus. California Med. **68**:35 (Jan.), 1948.

The author presents the case of a 7-year-old girl whose cardiac reserve was diminished by a patent ductus arteriosus. Ligation of the patent ductus arteriosus was carried out through a posterolateral incision, with removal of the left fourth rib. The ductus measured 1 cm. in diameter and 7 mm. in length. The thrill was completely obliterated after operation. The postoperative course was unsatisfactory from the outset because of infection. Atelectasis of the lower lobe of the left lung was observed on the roentgenogram of the chest twenty-four hours after operation and this consolidation increased within forty-eight hours. In seventy-two hours there was fluid in the left chest, and on the fifth day the amount of fluid had increased and had produced a shift of the mediastinum to the right. On the fourth postoperative day a murmur was heard over the pulmonic area, and on the ninth day this murmur had become definitely humming in character. On the tenth day the central portion of the incision was opened, old clots of blood were removed, and a tube was inserted for drainage. On the seventeenth day a portion of the ninth rib was resected and the mediastinum was explored with the finger. A large tube was inserted for continuous irrigation. Sulfadiazine, large doses of penicillin, and blood and serum transfusions failed to check the infection. The patient died on the twenty-second postoperative day.

Autopsy revealed an unexpected explanation for the re-establishment of communication between the aorta and the pulmonary artery. There was massive bilateral consolidation of both lungs and empyema on the left. The ductus lay as a necrotic cord within the ligatures. It was detached for three-quarters of its circumference from its attachment to the aorta and for one-third of its circumference from its attachment to the pulmonary artery, leaving round openings in both vessels. It was apparent that the ductus had become detached at its junctions with the main vessels and communication had become re-established between these two openings. The

detachment was probably due to tension on the wall of the ductus at the points of junction with the main vessels and necrosis of the ductus as a result of the ligation.

BELLET.

Farah, A., and Maresh, G.: Determination of the Therapeutic Irregularity and Lethal Doses of Cardiac Glycosides in the Heart-Lung Preparation of the Dog. J. Pharmacol. & Exper. Therap. **92**:32 (Jan.), 1948.

The authors found that, on a molar basis, the cardiac glycosides have the following order of decreasing potency: g-strophanthin, digoxin, digitoxin, oleandrin, and lanatoside B.

The average ratios of the dose producing cardiac irregularity to therapeutic dose, and lethal dose to therapeutic dose were the same for all five glycosides studied. These findings differ from other reports in which other methods and preparations were used.

GODFREY.

Farah, A., and Maresh, G.: The Influence of Sulfhydryl Compounds on Diuresis and Renal and Cardiac Circulatory Changes Caused by Mersalyl. J. Pharmacol. & Exper. Therap. **92**:73 (Jan.), 1948.

In a well-controlled series of experiments, using both anesthetized and unanesthetized animals of two species (rabbit and dog), the authors demonstrated that the diuresis caused by mersalyl was abruptly and completely inhibited by 2,3-dimercaptopropanol (BAL). The diuresis caused by intravenous infusion with sodium chloride and aminophylline was not inhibited by BAL. Cysteine hydrochloride and glutathione had no effect upon the diuresis of mersalyl even when given in very large doses.

BAL, cystein hydrochloride, and glutathione have all been found to be effective in inhibiting the cardiotoxic effects of mercurials.

To correlate the cardiotoxic inhibiting effects with the renal effects of BAL, cysteine hydrochloride, and glutathione, animals were given infusions of mersalyl and simultaneous records were made of blood pressure, electrocardiogram, and urinary output. When cardiotoxic manifestations occurred, the sulfhydryl compound was given intravenously. BAL was found to inhibit both the cardiotoxic effects and the diuretic effect of the mercurial. Cysteine hydrochloride and glutathione inhibited only the cardiotoxic action.

The characteristic diuresis caused by mersalyl is initiated by a transient reduction in urinary output. This was shown to be due to a reduction in kidney blood flow. This reduction in blood flow is completely abolished by all three of the sulfhydryl compounds (BAL, cysteine hydrochloride, and glutathione). Since only BAL inhibits the diuresis, the evidence suggests that mercurials affect more than one process in the renal excretory process.

GODFREY.

Spicknall, G. G., and Binford, C. H.: Healed Dissecting Aneurysm of the Aorta With Signs of Aortic Insufficiency. Mil. Surgeon **102**:47 (Jan.), 1948.

The authors report the case of a 48-year-old white man who was admitted to the hospital complaining of shortness of breath and swelling of the ankles. He had been hospitalized previously for similar complaints. During this hospitalization hypertension and generalized arteriosclerosis were found associated with evidence of myocardial damage and myocardial insufficiency. A to-and-fro murmur was heard at the aortic area and there was evidence of a moderate grade of congestive failure. His blood pressure was 204/92. Within a few weeks after admission he became progressively more stuporous; the blood urea nitrogen rose to 46.4 mg. per cent, and the blood creatinine, to 2.4 mg. per cent. He finally became comatose, developed a uremic odor to his breath, terminal convulsions, and died.

Autopsy revealed an aortic pouch which was classified macroscopically as dissecting aneurysm of the abortive or healed type. The exact mechanism of production of the aortic incompetency in this patient is not entirely clear, although it seems probable that the lower lip of the dissecting aneurysm interfered with the closure of the aortic valve leaflets and that the cusps did not meet

in diastole because of the displacement of the commissure between the right and posterior aortic cusps. A dissecting aneurysm was not considered in the differential diagnosis in this case, and the etiology of the patient's aortic insufficiency was thought to be syphilis even though his serologic tests for syphilis were negative.

BELLET.

Hayward, G. W.: Tetraethyl Ammonium Bromide in Hypertension and Hypertensive Heart-Failure. Lancet **1**:18 (Jan. 3), 1948

The present investigation was undertaken to determine whether the administration of tetra-ethyl-ammonium bromide (T.E.A.B.) would be a useful preoperative test in the selection of hypertensive patients for sympathectomy. By temporarily paralyzing the sympathetic ganglia and blocking the sympathetic vasoconstrictor impulses, tetra-ethyl-ammonium bromide might indicate whether release of vasoconstrictor tone is likely to produce a significant fall in blood pressure or not, and so help to eliminate those patients with permanent organic changes in the vessel wall who will be unsuitable for operation. In ten hypertensive patients who had a transthoracic splanchnic neurectomy performed, the blood pressure readings obtained preoperatively with tetra-ethyl-ammonium bromide and with sodium amytal have been compared with those found two weeks after the completion of the operation. Observations have also been made on the effects of administration of tetra-ethyl-ammonium bromide to patients with hypertensive heart failure.

In a preliminary group of thirty patients with essential hypertension, the comparative effects of tetra-ethyl-ammonium bromide and sodium amytal were studied. The average fall in blood pressure with tetra-ethyl-ammonium bromide was 58 mm. Hg systolic and 28 mm. Hg diastolic, as compared with 74 mm. Hg systolic and 35 mm. Hg diastolic with sodium amytal. Of the ten patients operated on (removal of the sympathetic chain and ganglia from D 6 to L 1), the operation led to fall in diastolic blood pressure of at least 20 mm. Hg in every case. The postoperative blood pressures recorded two weeks after the completion of the second stage of the operation were usually the lowest levels reached. The diastolic pressure in the preoperative test with tetra-ethyl-ammonium bromide agreed within 10 mm. Hg with the postoperative level in seven of the ten cases. With the sodium amytal test, agreement to a like degree was reached in nine of ten cases. The postoperative response of four patients to a subsequent or a similar dose of tetra-ethyl-ammonium bromide was investigated and in each case the blood pressure fell to a level lower than reached in the preoperative test.

In the present investigation there were no real toxic effects; apart from transient tingling, visual changes, and a feeling of weakness, the patients experienced no discomfort, provided they lay down for thirty minutes after the injection. In the selection of cases for operation it is important to have some preoperative test for liability of the blood pressure, the results of which agree fairly closely with the level of blood pressure found after operation. The tetra-ethyl-ammonium bromide test used in this investigation is safe, quick, and easy to carry out without discomfort to the patient. In patients with hypertensive heart failure, tetra-ethyl-ammonium bromide usually relieves orthopnea and dyspnea and causes the vital capacity, tidal air, and pulmonary ventilation per minute to increase and the venous pressure to fall. Because of its action in reducing pulmonary congestion, tetra-ethyl-ammonium bromide may be useful in the emergency treatment of paroxysmal nocturnal dyspnea or of acute pulmonary edema due to acute left ventricular failure.

BELLET.

Scheifley, C. H., and Hagedorn, A. B.: The Treatment of Subacute Bacterial Endocarditis: A Report of Forty Cases. Proc. Staff Meet. Mayo Clin. **23**:1 (Jan. 7), 1948.

The records of the penicillin-treated patients which had been seen at the Clinic were reviewed by the authors. There were forty patients for whom adequate follow-up data were obtained. Thirty-one of these patients were alive and symptom free after an interval which averaged sixteen months from the time treatment was stopped. This represents a survival rate of 77.5 per cent. The patients' ages averaged 38 years and varied from 9 to 73 years. The underlying

cardiac lesion was a rheumatic valvulitis in all but two of the patients who had congenital heart lesions. The etiological agent was a green-producing streptococcus in all except three persons in whom *Streptococcus faecalis* was responsible for the infection.

For the average patient, around 300,000 units of penicillin per day were given intramuscularly in divided doses every three hours, day and night, for a period of from three to six weeks. In more recent months, this was increased to 500,000 to 1,000,000 units per day for a period of from five to seven weeks. In the case of organisms showing a high resistance to penicillin in vitro, doses as high as 10,000,000 units a day were given by continuous intravenous drip for periods of from six to eight weeks before a cure could be effected.

Of the nine patients who died, four represented definite treatment failures. In three of the nine fatalities the cause of death was unknown, but two of these patients died within a period of three weeks after the treatment was stopped and most probably represented treatment failures. In two of the nine fatalities death resulted from congestive heart failure within two months after treatment was stopped, the disease having been bacteriologically arrested. Thus, of the nine who died, six represented treatment failures while three had achieved bacteriologic arrest of their infections. A minimum of three to four weeks of continuous therapy appears necessary. The daily dose of penicillin must be adequate; a minimal daily dose, usually 500,000 to 1,000,000 units per day, is sufficient in the ordinary case. The authors feel it is safe to predict that if therapy is started early and if it is sufficiently intensive, a remarkably high percentage of recoveries will be obtained.

BELLET.

Beaumont, G. E., and Hearn, J. B.: A Case of Reversible Papilloedema Due to Heart Failure. Brit. M. J. 1:50 (Jan. 10), 1948.

A man 61 years of age was admitted to the hospital with a diagnosis of coal-gas poisoning of two days' duration. Examination revealed some justification for this diagnosis since he was in a stuporous condition, extremely dyspneic, and very cyanosed, the hands and face being a deep blue-plum color. The blood pressure was 145/95. There were marked venous engorgement, a palpable liver, and râles at the base of both lungs. It was thought that this was a case of left- and right-sided heart failure, probably secondary to long-standing emphysema, bronchitis, and asthma. X-ray examination of the chest suggested that there was some pulmonary arteriosclerosis. On routine examination of the eyes the patient was found to have pronounced papilledema of both discs. The patient was treated by venesection "cardophylin," and digitalis, and in seven days all signs of heart failure had disappeared, with the exception of some residual cyanosis of the extremities, of the ears, and of the fingers. The papilledema gradually cleared. After improvement, the patient was discharged, the blood pressure having fallen to 100/75; but two months later he relapsed and died in a second attack of cardiac failure in which the bilateral papilledema was again present.

BELLET.

Draper, A. J., Jr.: Dicumarol Poisoning. J. A. M. A. 136:171 (Jan. 17), 1948.

The author presents a case of self-medication with Dicumarol which resulted in widespread hemorrhages of serious import.

A 46-year-old graduate nurse entered the hospital complaining of pain across the middle of the back, tightness in the upper part of the abdomen, and the passage of bloody urine for two days. The patient said she had taken "eight or ten tablets" of Dicumarol for "arthritis," three weeks prior to admission. Fleeting pains throughout the limbs and trunk when the patient arose in the morning led to the diagnosis of arthritis. Physical examination revealed scattered deep purple ecchymoses some 2.0 cm. in diameter over the skin of the forearms, thighs, and flanks. Scattered petechiae were easily seen over the chest, forearms, and calves and in the mucous membrane of the mouth. The bleeding time was 5 minutes 30 seconds, coagulation time, 10 minutes plus, and prothrombin time, 1 per cent. On the day following admission, the patient was given 30 mg. of Synkayvite (a vitamin K preparation) intramuscularly, in divided doses, 60 mg. of Synkayvite intravenously twice, six hours apart, and a transfusion of 500 c.c. of fresh citrated

whole blood. By the third day the patient showed much subjective improvement. The temperature beginning the day following admission rose daily but returned to normal levels by the eighth day. The prothrombin level rose successively and reached 55 per cent on the eighth day. The coagulation time fell by the fifth day to 2 minutes 6 seconds, and the bleeding time to 1 minute 15 seconds. Blood counts had been restored to normal by the seventh day. The patient was discharged on the eighth hospital day.

BELLET.

Warren, J. V., Brannon, E. S., Weens, H. S., and Stead, E. A., Jr.: Effect of Increasing the Blood Volume and Right Atrial Pressure on the Circulation of Normal Subjects by Intravenous Infusions. Am. J. Med. 4:193 (Feb.), 1948.

The effect of increasing the blood volume by the rapid intravenous administration of 5 per cent albumin solution and physiological saline solution in normal young volunteers was studied. The observations included right atrial pressure, cardiac output, arterial pressure, plasma proteins, hemoglobin content of the blood, plasma volume, and heart size by means of teleroentgenograms.

The authors found that the increase in blood volume consistently caused a rise in atrial pressure, but the cardiac output, arterial blood pressure, and pulse rate showed no consistent change. No demonstrable change in the transverse diameter of the heart occurred with variations in atrial pressure of approximately 125 mm. of water. They conclude that increasing the blood volume and atrial pressure throws no demonstrable mechanical burden on the circulation in normal subjects and suggest that this may also be true in patients with heart failure.

The question of why fluid tends to accumulate in the lungs to such a striking degree in patients with heart failure is discussed at length.

WOODS.

Leiter, L.: Renal Diseases: Some Facts and Problems. Ann. Int. Med. 28:229 (Feb.), 1948.

Based on newer concepts of renal disease and renal physiology, the author presents a modified classification of the nephropathies. He demonstrates that the integration of pathogenesis with the altered physiology of the lesions provides a rational approach in the therapeutic management of the various types of renal disease.

He divides the organic lesions of the kidney into the following: (1) glomerulonephritis, (2) glomerulonephrosis, (3) glomerulosclerosis, (4) glomerulitis, (5) pyelonephritis, (6) vascular, (7) tubular, and (8) congenital anomalies.

The functional classification he employs is as follows: (1) vasoconstriction, (2) tubulovascular, (3) tubular (hormonal), and (4) tubular (metabolic).

Since he considers the use of the diagnosis of focal glomerulonephritis to be very dangerous from the standpoint of both treatment and prognosis, he recommends the term glomerulitis as a substitute for focal glomerulonephritis. The immunologic mechanisms which might be responsible for the development of poststreptococcal glomerulonephritis are briefly discussed. The problem of diabetic glomerulosclerosis is briefly considered and emphasis is placed on the need for recognizing that this is not an infrequent lesion. The salt retention which is a prominent feature in patients with essential hypertension is related to hormonal factors as well as to a disturbance in renal hemodynamics secondary to a generalized neurogenic vascular derangement.

The physiology of the kidney in cardiac failure is reviewed and, on the basis of such knowledge, the author shows the rationale of salt restriction in the treatment of cardiac edema.

The late renal deaths in the crush syndrome after incompatible blood transfusion reaction, in postoperative reactions, in the so-called hepatorenal syndrome, various infections and intoxications, metabolic comas, and other conditions are attributed to reflex renal vasoconstriction with ischemia of the tubular epithelium. He favors the term tubulovascular syndrome for this disturbance and considers it synonymous with the terminology of lower nephron nephrosis used by other investigators. The dividing line between the tubulovascular functional disturbances and the organic chemical nephroses or necroses of tubules is a tenuous one, and, perhaps, of only

temporal or quantitative significance in many instances. The important unifying feature has been called "functional disorganization" of the kidney. The renal tubule loses its highly selective ability to reabsorb certain elements and to discard other substances in the glomerular filtrate. Salt, nonprotein nitrogen, glucose, water, acids, bases, etc., may diffuse back completely through the disorganized tubule, especially since, on the one hand, filtration is very low and on the other hand, there is often some blockage of distal and collecting tubules by casts, pigment, debris, sulfa, and so forth. Interstitial edema of the kidney, with a tense capsule, may add further to the functional confusion. The net result is severe oliguria or anuria and uremic coma, superimposed on the patient's other troubles. The disturbance is often not recognized unless urine volume and concentration and the blood chemistry have been closely watched by the physician during his preoccupation with the patient's cardiac, peripheral vascular, pulmonary, cerebral, or skeletal situation.

In kidney disease, urinary tract obstruction should be excluded by ureteral cathetheriation. Decapsulation, the use of the artificial kidney of Koiff, or peritoneal irrigation may be required when there is urgent need for heroic treatment. He stresses the fact that the first line of attack in the treatment of medical or surgical shock after pain, anoxia, and hemorrhage have been counteracted is meticulous provision of proper conditions and materials for kidney function, leaving nothing to guesswork. The twenty-four-hour urine volume, measured at each voiding or every six hours by catheter, may be far more important than the rectal temperature or the pulse rate. Decisions as to the need for parenteral fluids should be made several times in twenty-four hours.

The paper closes with a brief discussion of the specific tubular dysfunctions resulting from various other disturbances such as diabetes insipidus, Addison's disease of the adrenals, the Cushing syndrome, renal diabetes, the Fanconi syndrome, and acidotic osteomalacia.

WENDKOS.

McKinlay, C. A.: Allergic Carditis, Pericarditis, and Pleurisy. J. Lancet **68**:61 (Feb.), 1948.

The author presents a case of serum sickness associated with enlargement of the cardiac silhouette, pericarditis, and pleurisy.

A 21-year-old man was admitted to the hospital complaining of weakness, nausea and vomiting, chills, precordial pain, and dyspnea. About five hours before the onset of symptoms and seven hours before admission, he had received a prophylactic injection of tetanus antitoxin because of laceration of the right index finger. The treatment consisted of sedation with codeine and acetylsalicylic acid and intramuscular injections of penicillin, 30,000 units every three hours. The precordial ache lessened the morning following admission and the patient was discharged on the fourth hospital day with a diagnosis of serum sickness. Twenty-three days later a doctor noted for the first time a systolic murmur at the apex. Thirty-two days after onset of illness, the patient stated that the pain over the heart area had continued to trouble him. During this period of over a month he was not well, although he worked off and on and noticed that the pain was always aggravated by bending over.

The patient was readmitted to the hospital for treatment and further study. On the morning after admission a diffuse loud, to-and-fro friction rub was heard over the precordium throughout the cardiac cycle. The chest film showed diffuse cardiac enlargement. The following day, pain on breathing appeared. There also developed a pleural friction rub in the left chest and axilla with x-ray evidence of pleural effusion which had not been present twenty-four hours before. The patient improved strikingly within three days and became free from pain except for an occasional twinge in the left lower costal area. The pericardial friction rub disappeared during this period of abrupt improvement. The pleural friction likewise subsided. X-ray of the chest revealed partial clearing within five days and complete disappearance of the pleural effusion within six days of its onset; the size of the heart became normal within six days.

The authors feel that the cardiac and pleural manifestations were anaphylactic in origin.

BELLET.

Perera, G. A.: Diagnosis and Natural History of Hypertensive Vascular Disease. Am. J. Med. 4:416 (March), 1948.

The author first discusses the difficulties involved in the definition of hypertension and the impossibility of making a sharp differentiation between normotension and hypertension. The various factors which maintain blood pressure, as well as secondary regulatory mechanisms and the effect of underlying pathologic states unrelated to specific causes of hypertension, are outlined. From an analysis of the author's series of 2,000 unselected and apparently healthy men between the ages of 20 and 30 years, and from additional studies in the literature, it would appear that about 5 per cent of the adult population is afflicted with this disorder. A clear-cut family history of the disease occurs in 50 to 60 per cent of hypertensive persons.

From the records of 2,147 patients with established hypertensive vascular disease, 250 subjects were selected in whom adequate data were available from which to draw general conclusions as to the natural history of the disorder. These conclusions form the bulk of the report and emphasize that the first signs usually appear in youth and early adult life and that the average life expectancy is considerably longer than is generally assumed.

WOODS.

Scheinker, I. M.: Hypertensive Cerebral Swelling, a Characteristic Clinico-pathologic Syndrome. Ann. Int. Med. 28:630 (March), 1948.

The author analyzes the pathologic and clinical features of twelve cases of hypertensive brain disease characterized by a sudden onset and rapid progression of severe headache, drowsiness, confusion, restlessness, and delirium accompanied by signs of increased intracranial pressure, such as elevation of spinal fluid pressure and bilateral papilledema, and occasionally by convulsions, impairment of vision, and weakness of the extremities. The outstanding pathologic brain changes found in all cases consisted in a tremendous degree of cerebral swelling.

The gross findings were characterized by a considerable increase in volume of both hemispheres, flattening of the gyri, and narrowing or obliteration of the sulci; considerable enlargement of the central and subcortical white matter with consequent narrowing and compression of the cortical gray matter; loss of demarcation between white and gray matter; and decrease in size or complete obliteration of both lateral ventricles. In addition, there were disseminated ball hemorrhages in various regions of the brain tissue. Only occasionally were there massive hemorrhages. The pertinent histologic findings may be summarized thus: (1) parenchymatous changes with evidence of swelling of the nerve fibers, myelin sheaths, glia, and particularly of the obligodendroglia; (2) vascular alterations confined to the small veins and capillaries characterized (a) by congestion and stasis, and (b) by swelling and degeneration of the endothelial cells. These changes were predominant in the white matter. In addition, there were arteriolar changes characteristic of hypertensive arteriopathy. Only occasionally were there seen small focal areas of softening or glial scarring. The diffuse swelling of wide areas of cerebral tissue explains why the clinical symptomology occasionally resembles the acute manifestations of brain tumor.

Examination of the optic fundi revealed definite signs of papilledema ranging from blurring of the disc margins to pronounced swelling of from 3 to 4 diopters. The retina disclosed various stages of hypertensive retinopathy characterized by constriction and thickening of the retinal arterioles, cotton-wool exudate, recent and old hemorrhages, and venous congestion. In ten of the twelve cases the spinal fluid pressure was high, and in four cases the protein of the spinal fluid was above 130 mg. per cent. Signs and symptoms of impaired renal function were present in all cases. Repeated urinalyses disclosed albumin and casts in the majority of the cases. In only one case were there signs of hematuria. The blood urea nitrogen was in some cases moderately elevated. Only in three cases were there found levels above 100 mg. per cent. At autopsy the kidneys disclosed changes described as arteriolar nephrosclerosis in various stages of development. In but three cases were there changes characteristic of accelerated nephrosclerosis. In one instance the diagnosis of chronic glomerulonephritis was made, and in another instance the diagnosis of chronic pyelonephritis was made.

WENDKOS.

Rich, A. R.: A Hitherto Unrecognized Tendency to the Development of Widespread Pulmonary Vascular Obstruction in Patients With Congenital Pulmonary Stenosis (Tetralogy of Fallot). Bull. Johns Hopkins Hosp. **82**:389 (March), 1948.

The purpose of this report is to call attention to the unrecognized tendency of patients with congenital pulmonary stenosis to develop widespread obstruction of the pulmonary vascular bed. This condition was present in 90 per cent of twenty-one consecutive cases studied at autopsy.

There are two circumstances that may be expected to favor spontaneous thrombosis in the pulmonary tree in these patients. In the first place, the anoxemia due to the inadequate pulmonary circulation results in the development of a compensatory polycythemia, often of marked degree. Polycythemia is recognized as a condition favorable to thrombosis, apparently because of the increased viscosity of the blood (see the formation of "marantic" thrombi in patients with increased viscosity of the blood due to dehydration). In addition, patients with the tetralogy of Fallot are subject to another influence, not present in patients with polycythemia vera, which can favor the development of thrombosis in the pulmonary vessels, namely, the inadequate pulmonary blood flow that results from the pulmonary stenosis. Because of this additional factor favoring thrombosis in the pulmonary vascular bed, a patient with pulmonary stenosis having the same degree of polycythemia as one with polycythemia vera should be more likely to develop thrombosis of the pulmonary vessels.

Since patients with the tetralogy of Fallot suffer from a marked deficiency in the oxygenation of the blood due to the reduced flow of blood through the lungs, the presence of widespread thrombosis of the pulmonary vessels may well add to the difficulty of oxygenation.

BELLET.

Lichtenstein, L., and Sewall, S.: Pulmonary and Cerebral Fat Embolism Following Intravenous Administration of Ether Therapeutically. J. A. M. A. **136**:827 (March 13), 1948.

A fatality from fat embolism to the lungs and brain occurring during the course of intravenous administration of dilute ether solution for impending ischemic gangrene is reported. It is hypothesized by the authors that the fat emboli may have resulted from the liberation of free fat by the ether from the lipoid envelope of the erythrocytes or the emulsified fat of the plasma.

HANNO.

Ungar, H.: Diffuse Interstitial Myocarditis in a Case of Epidemic Encephalitis. Am. J. Clin. Path. **18**:4 (Jan.), 1948.

The author presents the case of a 65-year-old man who was admitted to the hospital in a semi-stuporous condition. The illness had begun quite suddenly with a temperature of 102.2° F. which had continued since that time. The patient's condition became rapidly worse; stupor deepened and respiration became more difficult. The patient died six days following admission, on the fourteenth day of his illness.

The significant findings at necropsy were nonpurulent epidemic encephalitis and nonpurlent interstitial myocarditis. The myocardium was of a dark reddish color and, in the wall of the left ventricle (especially in its lower portion and in the septum), showed many parallel, grayish streaks. Sections from all areas contained accumulations of cells which were mainly composed of small lymphocytes and occasionally also included a limited number of polymorphonuclear leucocytes. Histologic study of the brain revealed perivascular infiltrations of a character and a distribution held to be characteristic of acute epidemic encephalitis.

The author feels that a viral myocarditis was a probable cause of the described findings. He points to the growing list of viral diseases in which myocarditis has been shown to occur and to the fact that the histologic features in such cases were similar to those observed in this case.

BELLET.

Platt, R.: Heredity in Hypertension. Quart. J. Med. **16**:111 (July), 1947.

The author analyzed 116 cases of hypertension with a view to determining how many patients were without a family history of hypertension, the disease was not of the primary or essential type. The patients studied were divided into four groups: (1) those in whom the evidence of hypertension in one or both parents was strong, or if uncertain, was supported by a history of hypertensive disease in siblings of parents of patients; (2) those in whom the evidence of hypertension in either parent was lacking; (3) those in whom the evidence pointed only to a reasonable probability of hypertensive disease in one or both parents; and (4) those in whom the evidence was against hypertensive disease in either parent. In addition to the study of 116 cases, family histories were secured from seventy-one unselected patients without hypertension who were used as the control group.

This author found that approximately 76 per cent of the cases of essential hypertension gave a family history suggestive of hypertension, and in only 6.4 per cent did the family history appear to speak against hypertension. The data were not obtainable in the remainder. In the patients with secondary hypertension and in the control group the incidence of a positive family history was approximately 35 and 39 per cent, respectively.

Although it is impossible from the data available to state that essential hypertension is conveyed as a Mendelian dominant, the facts are compatible with the hypothesis that the great majority of cases in which the Mendelian rule does not seem to hold are not essential hypertension, and that careful investigation will reveal a hereditary factor in over 90 per cent of cases of essential hypertension in which the necessary data are obtainable.

BELLET.

Murray, G.: The Tetralogy of Fallot and Its Surgical Treatment. Brit. M. J. **2**:905 (Dec. 6), 1948.

The author feels that the patient with the tetralogy of Fallot most suitable for surgery is the child who has survived for perhaps a year or more, has limited exercise tolerance, and has the findings characteristic of this condition. The principle of surgical treatment is to take a large branch from the aorta and anastomose it with the pulmonary artery so that more blood passes through the pulmonary circulation. In Blalock's early series the mortality rate was about 25 per cent; but according to a more recent publication it has been reduced to 17 per cent. In the author's series of sixty cases of congenital heart disease treated surgically, there were forty of Fallot's tetralogy, eleven of patent ductus arteriosus, and nine others, with an over-all mortality of 11.7 per cent and in the tetralogy cases, 7.5 per cent. All the patients received heparin postoperatively to aid in keeping the anastomosis patent. The surgical treatment of many cases of the tetralogy of Fallot is very satisfactory, bringing relief of symptoms, improvement in color, and greatly increased vigor.

BELLET.

Russek, H. I., and Zohman, B. L.: Papaverine in Cerebral Angiospasm (Vascular Encephalopathy). J. A. M. A. **136**:930 (April 3), 1948.

In view of the proved effectiveness of papaverine hydrochloride as an arterial dilator in cases of arterial embolism, angina pectoris, and myocardial infarction, Russek and Zohman explored the use of this drug in the treatment of recurrent vascular encephalopathy.

A series of forty-six patients, both with and without hypertension, who presented recurring transient episodes of vascular encephalopathy were given papaverine hydrochloride by mouth in divided doses varying from 4½ to 18 grains daily. In most instances (exact figures are not given) continuous administration of the drug resulted in complete cessation of the attacks. The authors found that the concomitant use of small doses of phenobarbital (grains ¼ to ½ three times per day) appeared to reduce the amount of papaverine necessary for clinical improvement, whereas coffee and tea in excessive amounts seemed to be antagonistic to the beneficial action of the drug.

The authors state that vascular encephalopathy may occur in the absence of hypertension, and they point out that the favorable results of papaverine therapy would seem to indicate that

angiospasm may be the underlying disorder in the production of the vascular encephalopathic episode.

An additional unspecified number of patients with hypertensive headache and three patients with encephalopathy associated with acute glomerulonephritis responded favorably to oral papaverine; intravenous administration of the drug was effective in the treatment of two cases of retinal angiospasm in hypertensive patients.

It is suggested that papaverine may be of benefit in the encephalopathic episodes of eclampsia and lead poisoning.

HANNO.

Wang, S. C., and Borison, H. L.: Decussation of the Pathways in the Carotid Sinus Cardiovascular Reflex: An Example of the Principle of Convergence. Am. J. Physiol. **150**:722, 1947.

In completely sympathectomized dogs in which one vagus has been sectioned, stimulation of the carotid sinus on the vagotomized side still produces bradycardia. If the opposite vagus is also excluded, no cardiac slowing ensues. Stimulation on the side of the intact vagus is less effective than stimulation of both sinuses. As the effect of change in sympathetic tone has been eliminated by sympathectomy it appears that there is a definite crossed vagal component. Decerebration experiments make it likely that the level of decussation occurs in the spinal cord and below C_2.

The bradycardia following bilateral sinus distention is invariably greater then the sum of the reduction in heart rate obtained when the two sinuses are distended separately. It is argued that this phenomenon is similar to the "fascilitation" that is seen in spinal reflexes. Sinus depressor reflexes, on the other hand, demonstrate the "occlusion" phenomenon: fall in pressure upon bilateral sinus stimulation is much less than the hypotension induced by individual stimulation of the carotid sinus.

HECHT.

Hansen, P. F. and Faber, M.: Raynaud's Syndrome Originating From Reversible Precipitation of Protein. Acta med. Scandinav. **129**:81, 1947.

A 49-year-old woman with aleucemic plasma cell leucemia, running a one and one-half year course, developed as her initial symptom Raynaud attacks in the fingers and toes. Later she developed upon her face, trunk, and thigh patches of sharply circumscribed pallor which were brought on by chilling or local cold; the pallor was followed by blueness and erythema upon application of heat. These patches were painful and became progressively severe and frequent, so that preterminally the patient had to take several hot baths a day. Cavernous sinus thrombosis, retinal vein thrombosis, and loss of taste for cold food developed near the end of her course.

It was noted that her blood was difficult to smear. This proved to be due to whitish, sago-grain-sized bodies which precipitated when the blood ran at room temperature and could be seen passing along the side of containers. A "pearl necklace" effect was seen in the retinal vessels, consisting of lumps of red blood cells separated by constricted or colorless areas. The precipitation did not occur at body temperature. The substance concerned was found to be a euglobulin. Studies showed normal blood counts till near the end, and a high volume index (1.3 to 1.7), believed due to precipitation of protein with the red cells. The sedimentation rate was 2 to 6 mm. in one hour at room temperature and 145 mm. in forty-five minutes at body temperature. The serum protein total at 40° C. was 8.16, with albumin 3.96 and globulin 4.2 Gm. per cent, as opposed to 6.7 Gm. per cent total, with albumin 5.2 and globulin 1.5 at room temperature. The concentration of the euglobulin was calculated to be 2.25 Gm. per cent.

The author has seen no mention of vascular abnormalities in papers reporting abnormal protein precipitation in myelomatosis, kala azar, and other states associated with hyperglobulinemia. He believes the mechanism of the vascular abnormalities to be reversible embolism and distinguishes this process from changes in blood viscosity or vascular tone produced by cold. Ulnar nerve block did not relieve or prevent the digital attacks, which continued to be producible by cooling and reversible by heat. Plethysmography of affected fingers demonstrated

that during the "white" phase of an attack the amount of digital blood decreased markedly but pulsation remained normal, whereas in normal individuals cooling the fingers caused both decreased volume and disappearance of pulsation. This was also the consequence of cooling the proximal digital arteries while the tips of the fingers were kept warm in both the patient and the controls.

It is emphasized that though the phenomena this patient displayed were distinguishable from those of Raynaud's disease, they were sufficiently similar to be confusing. Cold-reversible embolism should be suspected in cases of Raynaud's syndrome that fail to subside spontaneously.

SAYEN.

Oehnell, R. F.: Pre-excitation and Auricular Fibrillation. Acta med. Scandinav. **129**:264, 1947.

The case is presented of a 59-year-old teacher who had suffered from episodes of paroxysmal auricular fibrillation and flutter for at least eight years. Anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome) was intermittently present during the periods of both normal and abnormal auricular rhythms. The abnormal QRS complexes were usually wider during the episodes of fibrillation than when sinus rhythm was present. The absence of demonstrable P waves during the periods of circus rhythm deprives the syndrome of one important diagnostic feature, the short P-R interval. Abnormal ventricular complexes occurring at such times cannot be differentiated from aberrant responses, true bundle branch block, or ventricular extrasystoles.

HECHT.

Rasmussen, H., and Nylin, G.: The Electrocardiogram in Mitral Stenosis With Special Regard to Its Development. Acta med. Scandinav. **129**:446 (No. V), 1948.

One hundred cases of mitral stenosis were studied. Most of these cases were severe, and many of the patients had had electrocardiograms made over a period of several years. Limb leads and sometimes a single chest lead were recorded. Sixty-eight per cent had auricular fibrillation.

The P waves were frequently split, most commonly in Lead II. Left axis deviation was found in 9 per cent, three patients having hypertension. Right axis deviation occurred in 26 per cent, eleven patients having right ventricular "retardation" and six, right bundle branch block. Many patients had abnormal R waves in Lead I; in only 31 per cent could this lead be considered completely normal.

The authors believe the "electrocardiographic development" consists of a progressive retardation of the right ventricular excitation which may cease at the stage of low R waves in Lead I or progress, as in 6 per cent of this group, to right bundle branch block. Since six per cent of another series of patients with left ventricular hypertrophy had left bundle branch block, it is suggested that the findings are in accord with the view that bundle branch block is most often due to enlargement of one of the ventricles.

SAYEN.

Wang, S. C., and Borison, H. L.: An Analysis of the Carotid Sinus Cardiovascular Reflex Mechanism. Am. J. Physiol. **150**:712, 1947.

In forty dogs anesthetized with Nembutal, the carotid sinuses were exposed and cannulated. The smaller vessels leading to and from the sinus were occluded by hemostatic globulin. The sinuses were stimulated by sudden increase of intrasinus pressures. This was accomplished by unclamping the tubing of a pressure bottle filled with saline which was connected to the indwelling cannula. It was demonstrated that (1) the combined effect of vagal and sympathetic components is always greatest immediately upon stimulation, (2) the vagus appears to be responsible for most of the immediate effects, and (3) the onset of decreased sympathetic activity is slow but accounts for most of the cardiac slowing if the stimulus is prolonged. The relatively rapid disappearance of the vagal slowing (adaptation) occurs even after exclusion of vagal afferent fibers. It appears that adaptation may be related in part to "vagal escape," that is, desensitization of the heart to the vagal effects.

HECHT.

O'Neill, J. F.: The Effects of Venous Endothelium on Alterations in Blood Flow Through the Vessels in Vein Walls, and the Possible Relation to Thrombosis. Ann. Surg. **126:**270 (Sept.), 1947.

The author developed a new technique of staining and mounting segments of vein wall which demonstrates with great sensitivity early changes in the endothelial cells of the vein in response to slowing of the intraluminal blood flow and to interference with the vasa venarum. In one series of experiments the femoral or jugular veins of dogs were isolated for several centimeters in order to divide the vasa venarum, and at periods of three to forty-eight hours after isolation, the veins were removed for study. The changes in the endothelial cells became more marked as the time of the period of isolation increased. In another series of experiments, metal clamps were placed around veins to narrow the lumen and hence produce partial stasis without severing the vasa venarum. The endothelial changes were less marked in severity by this technique, but in several experiments clots formed.

On the basis of his experiments, O'Neill discusses the possible relation of hypoxia and stasis to clinical venous thrombosis. Further experiments are outlined which will make use of these new techniques in the hope of arriving at a clearer understanding of the pathogenesis of venous thrombosis.

LORD.

Errata

In the paper, "The Mechanism of Irregular Sinus Rhythm in Auriculoventricular Heart Block" by Irving R. Roth, M.D., and Bruno Kisch, M.D., Am. Heart J. **36:**257 (August), 1948, a correction must be made. The last part of the title of Table IV on page 266 should read, "Cycles 1 to 11 of Tracing A are illustrated in Fig. 4."

In the paper entitled "Observations on the Effects on the Lungs of Respiratory Air Flow Resistance in Dogs With Special Reference to Vagotomy" by S. Zinberg, M.D., W. G. Kubicek, Ph.D., and M. B. Visscher, M.D., Am. Heart J. **35:**774 (May), 1948, a correction is necessary. In Fig. 1, page 775, the tube immersed in water should be connected to the opposite opening in the flask.

A correction is required in the paper entitled "A Simple Method of Determining Abnormalities of the Q-T Interval" by Emanuel Goldberger, M.D. Am. Heart J. **36:**141 (July), 1948. In the sentence which begins on the fifth line from the end of "Discussion" on page 143, it is stated that "the normal Q-T ratio can be as large as 1.09 for men and children and 1.12 for women." The figure 1.08 should be substituted for 1.09 and the figure 1.09 should be substituted for 1.12.

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RECOMMENDATIONS OF THE RESEARCH POLICY COMMITTEE

The following recommendations of the Research Policy Committee were approved in principle by the Board of Directors and Scientific Council of the American Heart Association. These recommendations have been circularized among the membership of the Scientific Council for their suggestions. Upon final approval by the Board of Directors, these policies will govern the allocations of funds for research purposes by the American Heart Association.

The ultimate aim is to develop a continuing program of productive research within the broad field of cardiovascular disease, and it is hoped that the need for such a program over the country as a whole, rather than in a few centers only, will be considered.

I. THE TRAINING AND SUPPORT OF MEN OF OUTSTANDING ABILITY

It is the opinion of this Committee, corroborated unanimously by numerous informed individuals with whom the problem has been discussed, that the greatest contribution which could be made to cardiovascular research would be provision for continuing careers for able investigators. It is recommended, therefore, that the American Heart Association undertake to support not only investigators in training, but also, as funds are available, undertake support of the full career of proved investigators.

There are three levels at which support is obviously needed, namely, Junior Fellows, Advanced Fellows, and Career Investigators. The support for the first category is most nearly adequate. It is therefore recommended that the American Heart Association, for the near future, devote its attention to the other two groups.

1. In regard to the *Advanced Fellowships*, the following suggestions are offered:

(a) Young persons of exceptional promise should be sought for through the usual channels, and also by the obtaining of information from the Welch Fellowship Board, the Markle Foundation, the Life Insurance Fund, the Public Health Service, the National Research Council, the Guggenheim Foundation, and from similar sources.

(b) Advanced Fellows should ordinarily be appointed for five years at an initial salary of $5,000 per annum, with an annual increase of $500 up to a maximum of $7,500. Adjustments in salary in line with changes in general costs of living would be appropriate. Under special circumstances, appointments might be made for periods of less than five years.

(c) There should be a yearly grant of $500 for supplies to the institution in which these Advanced Fellows work, and applications for additional grants-in-aid would be in order for consideration by the Research Allocation Committee as hereinafter recommended.

2. From among individuals who have held Advanced Fellowships or from among others of proved outstanding ability, *Career Investigators* may be selected and appointed, subject to the following conditions:

(a) It should be the intent of the American Heart Association to provide continuing support for adequate salary and budget for the duration of a normal working career, plus reasonable provision for retirement or disability.

(b) In order to safeguard against the unusual contingency of an individual's failing to live up to the promise of his earlier career, it should be provided that the American Heart Association

may, after arranging for proper investigation by qualified experts, terminate the appointment on one year notice at any time before the incumbent has reached the age of fifty-five, providing further that the American Heart Association shall be responsible for an additional four years for meeting any adverse difference in gross income.

(c) The Career Investigator will be expected to spend at least 75 per cent of his time in research fundamentally related to problems of the cardiovascular system.

(d) In making appointments of Career Investigators, the American Heart Association should publicize the availability of positions and should invite applications from individuals, as well as applications from institutions which desire such Investigators and are willing to provide facilities. The institution to which the Investigator is attached should be approved by the American Heart Association.

II. GENERAL PRINCIPLES REGARDING GRANTS-IN-AID

1. Provisions should be made for grants for periods ranging from one to five years.
2. It should be understood that grants are not to be used to replace any obligations currently assumed by the institutions receiving the grants.
3. The desirability of a given grant should be judged primarily by the likelihood of fruitful accomplishment, as indicated by (a) the investigator; (b) the program; and (c) the soundness of the policies of the institution and its willingness to provide the necessary physical facilities, and to share financial obligations for the support of the project.
4. The advantages to be derived from developing additional intellectual centers for cardiovascular research over the country as a whole should be considered.
5. Discoveries resulting from projects supported in whole or in part by funds of the American Heart Association should be publicized through the usual channels and should not be subject to patent.

III. FLUID GRANTS

It is recommended that either now, or when more adequate funds are available, the American Heart Association undertake the policy of providing fluid research grants in the cardiovascular field for suitable institutions. It is recommended that such a fluid grant should be administered in each institution by a small committee of investigators, nominated by the administrative officer, and approved by the American Heart Association.

The availability of such fluid research funds should be publicized and institutions should be invited to make application on the basis of their needs, personnel, and facilities.

IV. COMPOSITION AND DUTIES OF THE RESEARCH ALLOCATION COMMITTEE

1. It is recommended that this Committee consist of eleven men who shall elect annually a chairman who shall appoint from among personnel of the Committee such subcommittees as may be needed.
2. It is recommended that the term of service on the Committee shall eventually be five years, but that the initial membership be staggered with three men to serve for three years, and two men to serve for one, two, four, and five years, respectively. Any man who, having been appointed for five years, has served the full period shall be permanently ineligible for reappointment. However, an individual whose initial appointment was for less than five years is subject to reappointment for five years. Thus, in the beginning, the personnel of the Committee will necessarily have changed completely at the end of nine years, and eventually the personnel will change completely over five-year periods.
3. All recommendations made by this Committee must be approved by the appropriate governing bodies of the American Heart Association before becoming effective.
4. The Committee should be selected on a wide geographic basis.
5. There should be on the Committee individuals with research experience and interest in (a) arteriosclerosis, (b) hypertension, (c) rheumatic fever, (d) peripheral vascular disease, including vascular surgery, (e) pathological physiology, (f) basic scientific disciplines, and (g) at least one individual engaged in the practice of medicine in the cardiovascular field.

6. Persons who are currently serving on other Research Allocation Committees shall be ineligible for membership on this Committee. However, either the chairman or a subcommittee should consult frequently with representatives of other agencies which are supporting research in the cardiovascular field.

V. ALTERATIONS IN RESEARCH ALLOCATION POLICY

It is believed that the Research Allocation Committee should function under these general policies until they have been altered. However, one of the functions of the Committee should be to make recommendations to the governing bodies concerning changes in allocation policy.

APPLICATIONS FOR RESEARCH GRANTS

Dr. Irvine H. Page, Chairman of the Medical Advisory Council of the American Foundation for High Blood Pressure, has announced that applications for grants for research in hypertension and arteriosclerosis may be made to the Chairman of the Allocations Committee, Dr. Harry Goldblatt, Cedars of Lebanon Hospital, Los Angeles. Other members of the Committee are Dr. Thomas Addis, San Francisco, and Dr. William Dock, Brooklyn.

AMERICAN SOCIETY FOR STUDY OF ARTERIOSCLEROSIS

The annual scientific meeting of the American Society for the Study of Arteriosclerosis will be held on Oct. 31 and Nov. 1, 1948, at the Hotel Knickerbocker in Chicago.

Newly elected officers of the Society include Dr. William B. Kountz, St. Louis, President; Dr. Irvine H. Page, Cleveland, Vice-President; and Dr. O. J. Pollak, Quincy, Mass., Secretary-Treasurer. Directors include Dr. G. Lyman Duff, Montreal; Dr. Robert A. Katz, New Orleans; Dr. E. Cowles Andrus, Baltimore; Dr. Myron Prinzmetal, Los Angeles; Dr. Louis N. Katz, Chicago; and Dr. Henry S. Simms, New York.

American Society for the Study of Arteriosclerosis

PROGRAM OF THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

TO BE HELD IN

CHICAGO, ILL., OCT. 31 AND NOV. 1, 1948

October 31, 1948

Morning

(William B. Kountz, Presiding)

9:30– 9:40 Opening Session

9:40– 9:55 **Further Studies on the Fat-Depositing Mechanism**
Henry S. Simms, Mary S. Parshley, Ruth B. Pitt, and Joan B. Fulton, Columbia University College of Physicians and Surgeons, New York, N. Y.

9:55–10:00 Discussion

10:00–10:15 **The Inhibition of Experimental Cholesterol Atherosclerosis By Alloxan Diabetes in the Rabbit**
G. Lyman Duff and Gardner C. McMillan, Department of Pathology, McGill University, Montreal, Canada.

10:15–10:20 Discussion

10:20–10:35 **Hypertension and Coronary Thrombosis**
J. C. Paterson and R. B. Holmes, Department of Pathology, University of Western Ontario, London, Canada.

10:35–10:40 Discussion

10:40–10:55 **Cerebral Vascular Changes in Arterial Hypertension**
I. Mark Scheinker, Laboratory of Neuropathology, University of Cincinnati College of Medicine, Cincinnati, Ohio.

10:55–11:00 Discussion

11:00–11:45 **Some Aspects of the Intermediary Metabolism of Cholesterol**
Konrad Bloch, University of Chicago, Chicago, Ill.

11:45–12:00 Discussion

Afternoon

(Irvine H. Page, Presiding)

2:00– 2:30 Business Session

2:30– 2:45 **The Relationship Between Dietary Composition and the Blood Cholesterol Level**
Charles F. Wilkinson, Jr., Elmira Blecha, and Ann Reimer, University of Michigan Medical School, Ann Arbor, Mich.

2:45– 2:50 Discussion

2:50– 3:05 **The Effect of a Low Fat Diet on the Spontaneously Occurring Arteriosclerosis of the Chicken**
Louis Horlick, L. N. Katz, and Jeremiah Stamler, Cardiovascular Department, Michael Reese Hospital, Chicago, Ill.

3:05– 3:10 Discussion

3:10– 3:25 **Development of Atheromatous Plaques Following Production of Intimal Atherosclerosis by Intravenous Injection of Colloidal Cholesterol Into Rabbits**

Margaret Bevans, Forrest E. Kendall, and Liese Lewis Abell, Goldwater Memorial Hospital, New York, N. Y.

3:25– 3:30 Discussion

3:30– 3:45 **The Effect of Blood Cholesterol Disorders on the Coronary Arteries and the Aorta**

Lester M. Morrison and William F. Gonzales, Los Angeles County Hospital and the Department of Internal Medicine, College of Medical Evangelists, Los Angeles, Calif.

3:45– 3:50 Discussion

3:50– 4:05 **The Clinical Diagnosis of Arteriosclerosis**

William H. Davis, Two Harbors Hospital, Two Harbors, Minn.

4:05– 4:10 Discussion

4:10– 4:25 **Clinical Significance of Blood Cholesterol**

Harry E. Ungerleider and Richard Gubner, Medical Department, Equitable Life Assurance Society of the United States, New York, N. Y.

4:25– 4:30 Discussion

4:30– 4:45 **Studies on the Cholesterol Content of the Coronary Arteries and the Blood in Acute Coronary Thrombosis**

Lester M. Morrison, Albert L. Chaney, Charles Langmade, and W. A. Johnson, Los Angeles County Hospital, Los Angeles, Calif.

4:45– 4:50 Discussion

November 1, 1948

Morning

(E. Cowles Andrus, Presiding)

9:30– 9:40 Opening Session

9:40– 9:55 **Changes in Blood Cholesterol Levels in Patients With Coronary Occlusion Following Choline Therapy**

Lester M. Morrison, Lillian Hall, and William Gonzales, Los Angeles County Hospital, Los Angeles, Calif.

9:55–10:00 Discussion

10:00–10:15 **Reactions of the Coronary Arteries of the Dog Following Injury by Allylamine**

L. L. Waters and W. B. McAllister, Department of Pathology, Yale University School of Medicine, New Haven, Conn.

10:15–10:20 Discussion

10:20–10:35 **An Evaluation of Thyroid Function in Older Individuals With Various Degrees of Arteriosclerosis**

William B. Kountz, Margaret Chieffi, and Esben Kirk, Division of Gerontology, Washington University School of Medicine and St. Louis City Infirmary Hospital, St. Louis, Mo.

10:35–10:40 Discussion

10:40–10:55 **Radiocardiography: A New Method for the Study of the Circulation**

Myron Prinzmetal, Eliot Corday, Ramon Spritzler, and H. C. Bergman, Cedars of Lebanon Hospital, Los Angeles, Calif.

10:55–11:00 Discussion

11:00–11:15 **Studies on the Relationship of Diet and Renal Insufficiency to Arterial Disease**
Russell L. Holman, Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.

11:15–11:20 Discussion

11:20–11:35 **Further Studies on the Production of Arteriosclerosis in Dogs by Cholesterol and Thiouracil Feeding**
Alfred Steiner, J. D. Davidson, and Forrest E. Kendall, Goldwater Memorial Hospital, New York, N. Y.

11:35–11:40 Discussion

Afternoon

(O. J. Pollak, Presiding)

2:00– 2:15 **Sympathectomy for Arteriosclerosis Obliterans. Rationale and Results**
Alexander Blain III, Kenneth N. Campbell, and Bradley M. Harris, Department of Surgery, Alexander Blain Hospital, Detroit, and University Hospitals, Ann Arbor, Mich.

2:15– 2:20 Discussion

2:20– 2:35 **Lumbar Ganglionectomy in Peripheral Arteriosclerosis**
Leon Gerber, William S. McCune, and William Eastman, Surgical Service, George Washington University School of Medicine, and Gallinger Municipal Hospital, Washington, D. C.

2:35– 2:40 Discussion

2:40– 2:55 **Glomerular Lipoidosis in Intercapillary Glomerulosclerosis**
S. L. Wilens, S. Elster, and J. Baker, Department of Pathology, New York University College of Medicine, New York, N. Y.

2:55– 3:00 Discussion

3:00– 3:15 **The Prevention of Experimental Atherosclerosis by Choline Feedings**
Lester M. Morrison and Amerigo Rossi, Hunterian Laboratory, Department of Experimental and Internal Medicine, College of Medical Evangelists, Los Angeles, Calif.

3:15– 3:20 Discussion

3:20– 3:35 **The Absorption of Aortic Atherosclerosis by Choline Feedings**
Lester M. Morrison and Amerigo Rossi, Hunterian Laboratory, Department of Experimental and Internal Medicine, College of Medical Evangelists, Los Angeles, Calif.

3:35– 3:40 Discussion

3:40– 3:55 **Dissecting Aneurysms of the Aorta**
Jakub G. Schlichter, G. D. Amromin, and A. J. L. Solway, Pathology and Cardiovascular Departments, Michael Reese Hospital, Chicago, Ill.

3:55– 4:00 Discussion

4:00– 4:15 **New Experiments in Arteriosclerosis**
Rudolf Altschul, University of Saskatchewan, Saskatoon, Canada.

4:15– 4:20 Discussion

4:20– 4:35 **The Clinical Diagnosis of Arteriosclerosis With Particular Reference to the Use of the Roentgen Ray**
Frederic D. Zeman and Max Schenck, New York, N. Y.

4:35– 4:40 Discussion

4:40– 5:00 Closing Session

FURTHER STUDIES ON THE FAT-DEPOSITING MECHANISM

HENRY S. SIMMS, MARY S. PARSHLEY, RUTH B. PITT, AND JOAN B. FULTON, NEW YORK, N. Y.

Columbia University College of Physicians and Surgeons

It has been reported previously that blood serum contains lipoid materials called "lipfanogens" that are taken up by living cells and are converted into visible fat. Serum also contains an "antilipfanogen" which prevents fat deposition in proportion to its relative concentration.

The antilipfanogen is contained in Cohn's Albumin "Fraction V." On refractionating this material at low temperature and low ionic strength, we obtain high antilipfanogen activity in the precipitate formed at pH 5.2 with 40 per cent to 50 per cent alcohol. Relatively inert material is first precipitated at pH 5.8 with 30 per cent to 40 per cent alcohol.

There is no correlation between the lipfanogen concentration in serum and its analyzable lipoid constituents (total lipoids; phospholipoids; total, free, or ester cholesterol).

On the other hand, antilipfanogen has a negative correlation with the serum cholesterol (both ester and free) and also with the phospholipoids. In nephrosis and diabetes, where the cholesterol is high, the antilipfanogen is low. In individuals with low blood cholesterol, the antilipfanogen is high.

Administration of thyroid extract appears to increase the antilipfanogen. Depancreatized dogs are being used to study the relation of antilipfanogen to blood lipoids in experimental diabetes.

THE INHIBITION OF EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS BY ALLOXAN DIABETES IN THE RABBIT

G. LYMAN DUFF AND GARDNER C. MCMILLAN, MONTREAL, CANADA

Department of Pathology, McGill University

A comparison was made of the effects of cholesterol feeding in normal rabbits and in rabbits rendered persistently diabetic by means of alloxan. In both groups of animals, hypercholesterolemia of comparable degree was induced by the feeding procedure. Nevertheless, the severity of the experimental atherosclerosis of the aorta produced in the diabetic rabbits was much less than in the nondiabetic control animals. Indeed, a large proportion of the diabetic animals presented no atherosclerosis whatever. There was a similar inhibition of the deposit of lipid substance in the liver, spleen, and adrenal glands of the diabetic rabbits.

The inhibitory effect of alloxan diabetes on the development of experimental cholesterol atherosclerosis was independent of the administration of alloxan *per se*. The effect was not dependent on the sex or weight of the animal, nor upon the daily dosage of cholesterol, the form in which it was administered, nor the duration of cholesterol feeding. It was also independent of changes in body weight occuring during the course of our experiments and of the actual degree of hypercholesterolemia induced by the administration of cholesterol. In addition, there was no gross or histologic evidence of a morphologic basis for the inhibitory effect either in the aorta or in the other organs in which it was observed.

Only two factors were observed to be consistently associated with the inhibition of the expected morphologic effects of cholesterol feeding; namely, the diabetic state and a degree of visible lipemia considerably greater than that observed in the control animals.

We are quite unable to offer a specific explanation of the inhibitory effect observed in these experiments, but it would appear to depend upon some as yet undetermined factor or factors implicit in the diabetic state. The experimental data presented indicate clearly that hypercholesterolemia *per se* is not the sole factor concerned in the genesis of experimental cholesterol atherosclerosis, but that another factor or factors rendered inoperative by the diabetic state must be essential to the production of the arterial lesions.

The experimental procedures that we have employed provide a basis for the design of further experiments directed toward the elucidation of the nature of these unknown factors.

HYPERTENSION AND CORONARY THROMBOSIS

J. C. Paterson and R. B. Holmes, London, Canada
Department of Pathology, University of Western Ontario

The evidence is reviewed that the common precipitating lesion of a coronary thrombus is the liberation of thromboplastic substances from a disruptive haemorrhagic lesion in an atherosclerotic plaque of a coronary artery. Intimal haemorrhages are intrinsic lesions and are due to the rupture of newly formed capillaries that arise from the main arterial lumen. The possible causes of rupture of capillaries of this type are discussed; and it is postulated that if high blood pressure is a factor, intimal haemorrhages should be more frequent in hypertensive than in nonhypertensive individuals. Morphologic evidence is submitted to show that this is true.

CEREBRAL VASCULAR CHANGES IN ARTERIAL HYPERTENSION

I. Mark Scheinker, Cincinnati, Ohio
Laboratory of Neuropathology, University of Cincinnati College of Medicine

The present study aims to analyse the various types of vascular changes of the central nervous system in instances of arterial hypertension. A clinicopathologic study of 365 patients with arterial hypertension, complicated by a series of cerebral manifestations, form the material for the present study.

Attention is called to capillary changes characteristic of the *early* stage of the disease. The histologic changes typical of hypertensive arteriolopathy and their differentiation from arteriosclerosis are discussed in detail.

In addition to arteriolar changes, the following two types of venous alterations are described: (a) Reversible changes characterized by stasis congestion and distention of the vascular lumina and (b) Structural lesions of the vessel wall manifested by advanced signs of degeneration, necrosis, and an extreme degree of atrophy.

Whereas, the arteriolar changes are interpreted as significant for the disseminated foci of softening and gliosis of the nervous parenchyma, typical of chronic hypertensive encephalopathy, the alterations of the cerebral veins are regarded as responsible for the origin and pathogenesis of massive intracerebral hemorrhage so often encountered during the terminal phase of hypertensive brain disease.

SOME ASPECTS OF THE INTERMEDIARY METABOLISM OF CHOLESTEROL

KONRAD BLOCH, CHICAGO, ILL.

University of Chicago

The application of modern techniques to the study of biochemical processes has led to considerable advances in our understanding of various phases of intermediary lipid metabolism. In this respect the tracer method has been of particular value by permitting the study of cholesterol synthesis in intact animals as well as in isolated tissues. Thus, the mechanism of cholesterol synthesis has been shown to involve molecules of small size as precursors, notably acetic acid. Rate studies with intact animals and experiments with isolated tissues have demonstrated the prominent role of the liver as the site of cholesterol synthesis.

Animal tissues contain a variety of compounds which, like cholesterol, possess a steroid structure but differ widely with respect to their function in metabolism. The role of cholesterol as a precursor for other steroids has been experimentally demonstrated so far for two types of compounds: the bile acids and one of the steroid hormones (progesterone).

Interest in the relation of cholesterol metabolism to cardiovascular disease arises primarily from the fact that atheromatous aortas have an abnormally high content of cholesterol. Few attempts have been made to consider this problem in the light of intermediary cholesterol metabolism. It is conceivable that such problems as cholesterol transport, cholesterol catabolism, or the regulation of the rate of cholesterol synthesis are controlling factors in pathologic lipid deposition.

THE RELATIONSHIP BETWEEN DIETARY COMPOSITION AND THE BLOOD CHOLESTEROL LEVEL

CHARLES F. WILKINSON, JR., ELMIRA BLECHA, AND ANN REIMER, ANN ARBOR, MICH.

University of Michigan Medical School

Ninety-one individuals eating a diet of choice were studied. The cholesterol and other lipid levels of their blood were determined and from records kept over a period of time, the composition of their diet (carbohydrate, fat, protein, cholesterol, vitamins, calories, and minerals) was estimated.

Nineteen of these subjects had the metabolic disorder, essential familial hypercholesterolemia; the remainder were normal subjects. An analysis was made to determine whether a relationship between dietary composition and blood cholesterol could be established in either group.

Intake of carbohydrate, fat, protein, and cholesterol seem to have no effect on blood cholesterol; their influence on arteriosclerosis and life expectancy is discussed.

Our results, in many respects, do not agree with theories proposed in the past. However, no comparable set of data has been collected.

THE EFFECT OF A LOW FAT DIET ON THE SPONTANEOUSLY OCCURRING ARTERIOSCLEROSIS OF THE CHICKEN

LOUIS HORLICK, LOUIS N. KATZ, AND JEREMIAH STAMLER, CHICAGO, ILL.

The Cardiovascular Department, Medical Research Institute, Michael Reese Hospital

Spontaneous arteriosclerosis which resembles that seen in man has been reported to occur in 40 per cent of chickens over one year of age, and in more than 75 per cent at two years of age. We attempted to observe the effects on the frequency of occurrence and severity of the spontaneous lesions in chickens fed a diet very low in fat and liberally supplemented with vitamins.

Sixteen white leghorn cockerels were fed a diet of chick starter mash which contained 5 per cent of crude fat. Fourteen cockerels received an isocaloric mash diet with the fat content reduced to 0.3 per cent by repeated alcohol-ether extraction, and with supplements of vitamins A, B, D, and E added. The period of feeding ranged up to sixty-three weeks. Gross arteriosclerotic lesions occurred in the aortas of 63 per cent of the birds on the control diet and in 35 per cent of the birds on the low fat diet. The lesions occurred earlier and were more extensive and severe in the group receiving the normal chick starter mash. On microscopic examination fibrocellular proliferation and fat deposition were found in the intima of the aorta in both groups. The incidence of microscopic lesions was the same in both groups.

Plasma cholesterol, fatty acids, and lipid phosphorous were consistently slightly higher in the low fat group than in the control group. Complete lipid analyses of the livers and carcasses and fecal fat determinations were also done.

In this small series, restriction of fat did not prevent the development of spontaneous arterial lesions, but appeared to lessen the severity of the lesions when a parallel group on ordinary mash diet were compared.

DEVELOPMENT OF ATHEROMATOUS PLAQUES FOLLOWING PRODUCTION OF INTIMAL ATHEROSCLEROSIS BY INTRAVENOUS INJECTION OF COLLOIDAL CHOLESTEROL INTO RABBITS

MARGARET BEVANS, FORREST E. KENDALL, AND LIESE LEWIS ABELL, NEW YORK, N. Y.

Goldwater Memorial Hospital, Welfare Island

The effect of single and multiple intravenous injections of colloidal solutions of cholesterol into rabbits was studied. It was found that 25 ml. of a solution containing 0.5 Gm. of cholesterol, stabilized with 0.1 Gm. sodium stearate introduced into a rabbit weighing 2.5 kilograms will raise the serum cholesterol level about 250 mg. per cent ten minutes after the injection. The level drops rapidly at first but values in excess of the base line level may persist for as long as one week. Repeated injections lead to serum levels comparable to those obtained when the same amount of cholesterol is fed and result in atheromatous lesions indistinguishable from those produced in feeding experiments. The intravenous technique affords an unusual opportunity to study the sequence of events which lead to the formation of atheromatous plaques. Lipid can be detected within the intima of the aorta three hours after a single injection. Gross lesions are first noted at the end of twelve daily injections.

THE EFFECT OF BLOOD CHOLESTEROL DISORDERS ON THE CORONARY ARTERIES AND THE AORTA

LESTER M. MORRISON AND WILLIAM F. GONZALES, LOS ANGELES, CALIF.

Los Angeles County Hospital and the Department of Internal Medicine, College of Medical Evangelists

An appreciable increase in the incidence of coronary arteriosclerosis and aortic atherosclerosis is described in a disease associated with chronic hypercholesterolemia; an appreciable decrease in the incidence of coronary arteriosclerosis and aortic atherosclerosis is described in a disease associated with chronic hypocholesterolemia.

It is suggested from these studies that disturbances in cholesterol metabolism may be etiologic factors in the development of coronary arteriosclerosis and aortic atherosclerosis in human subjects.

THE CLINICAL DIAGNOSIS OF ARTERIOSCLEROSIS

WILLIAM H. DAVIS, TWO HARBORS, MINN.

Two Harbors Hospital

It is the impression of the writer that no clearly defined and universally agreed upon criteria exist for making a clinical diagnosis of arteriosclerosis, and that little importance has been given in the past to the etiologic types and pathologic forms in making such a diagnosis.

In this paper the author has reviewed the significant literature and attempted to compile all clinically useful material from this source and from practice. Emphasis has been placed upon the means for diagnosing the condition early in its course.

The paper is presented as a survey and introductory report, with the hope that it will stimulate criticism and also further consideration and investigation of a heretofore poorly defined and often neglected phase of diagnostics.

CLINICAL SIGNIFICANCE OF BLOOD CHOLESTEROL

HARRY E. UNGERLEIDER AND RICHARD GUBNER, NEW YORK, N. Y.

Medical Department, Equitable Life Assurance Society of the United States

Several studies have indicated that hypercholesterolemia occurs frequently in arteriosclerotic heart disease, but it has not been ascertained whether hypercholesterolemia is an etiologic factor in human arteriosclerosis or merely a concomitant of associated metabolic disorders (such as diabetes mellitus) which are responsible for degenerative vascular changes.

An analysis has been made of 104 insurance applicants with levels of blood cholesterol below 175 mg. per cent and 104 individuals with blood cholesterol above 260 mg. per cent. In addition to physical examination, blood sugar tolerance studies and electrocardiograms and teleroentgenograms were made on all subjects. Comparison is made between age, weight and body build, sugar tolerance, and the incidence of cardiovascular impairments in the group with low blood cholesterol values and the group with hypercholesterolemia. Included among cardiovascular impairment studied are abnormal blood pressure, heart murmurs, cardiac enlargement, electrocardiographic abnormalities, and roentgenologic evidence of arteriosclerosis of the aorta. No striking difference in the incidence of cardiovascular impairments between the two groups was found.

Although there is much evidence that cholesterol plays an important role in arteriosclerosis, it appears that hypercholesterolemia must be protracted over many years before vascular damage results, and that cholesterol is not the sole factor in the genesis of arteriosclerosis.

STUDIES ON THE CHOLESTEROL CONTENT OF THE CORONARY ARTERIES AND THE BLOOD IN ACUTE CORONARY THROMBOSIS

LESTER M. MORRISON, ALBERT L. CHANEY, CHARLES LANGMADE, AND W. A. JOHNSON, LOS ANGELES, CALIF.

Los Angeles County Hospital

In this study two groups of patients who had died from (a) acute coronary thrombosis and (b) non-"coronary" deaths were examined, post-mortem, to determine (1) the cholesterol content of the occluded artery and (2) the cholesterol and ester fraction of the blood. Correlations are demonstrated between (1) and (2) and their significance discussed.

CHANGES IN BLOOD CHOLESTEROL LEVELS IN PATIENTS WITH CORONARY OCCLUSION FOLLOWING CHOLINE THERAPY

LESTER M. MORRISON, LILLIAN HALL, AND WILLIAM GONZALES, LOS ANGELES, CALIF.

Los Angeles County Hospital

Over 100 patients have been treated with choline at regular intervals over a two-year period. The changes in blood cholesterol levels are presented and their significance discussed.

REACTIONS OF THE CORONARY ARTERIES OF THE DOG FOLLOWING INJURY BY ALLYLAMINE

L. L. WATERS AND W. B. MCALLISTER, NEW HAVEN, CONN.

Department of Pathology, Yale University School of Medicine

Coronary arteries of dogs have been injured by intravenous and intrapericardial injections of allylamine. The injury consists of acute necrosis of the vessel wall, reproducing many of the vascular changes seen in disease in man. Examples of the acute and chronic stages of the lesions will be shown and their pathogenesis discussed. Particulate substances, including lipids, introduced intravenously, tend to localize in the artery wall at the site of allylamine injury. Illustrations of this process will be provided.

AN EVALUATION OF THYROID FUNCTION IN OLDER INDIVIDUALS WITH VARIOUS DEGREES OF ARTERIOSCLEROSIS

WILLIAM B. KOUNTZ, MARGARET CHIEFFI, AND ESBEN KIRK, ST. LOUIS, MO.

Division of Gerontology, Washington University School of Medicine and St. Louis City Infirmary Hospital

Previous work indicates that there may be a direct or indirect relationship between decreased thyroid function and the occurrence of arteriosclerosis. Oxygen consumption as is measured by the basal metabolism has been used as an index to thyroid disorders. Likewise, increased blood cholesterol levels induced in experimental animals, especially Herbivora, lead to an abnormal deposit of cholesterol in the blood vessel walls. There is some indication that in man a high cholesterol level, such as occurs in hypothyroidism and other conditions, may lead to a similar process.

Previous studies from our laboratory have demonstrated an unstableness of the rate of oxygen consumption in older individuals with degenerative disease. This finding makes it difficult to draw definite conclusions from the basal metabolic rate concerning the degree of thyroid function in older individuals who may have arteriosclerosis. Likewise, it has been demonstrated in our laboratory that the cholesterol concentration of serum shows no close correlation with the basal metabolic rate and that both men and women with calcification of the peripheral arteries may have a lower cholesterol level than patients without calcification. Since factors other than hypothyroidism are believed to influence the cholesterol level, we feel that this may not be used as an index to thyroid function. A more reliable indication would be a determination of the concentration of organic iodine in the serum, since this is regarded as an expression of the activity of the gland.

Studies, therefore, were undertaken on middle-aged and old individuals with the purpose of correlating the organic serum iodine value and the degree of arteriosclerosis. It is felt that this technique will throw more light on the rate of thyroid function in arterial degeneration. All patients investigated were subjected to a thorough study from the point of view of history, physical and laboratory findings. Repeated determinations of the basal oxygen consumption were performed, using a Sanborn apparatus, the accuracy of which was checked by alcohol combustion.

The evaluation of the three methods of study of thyroid function and the results and conclusions will be presented.

RADIOCARDIOGRAPHY: A NEW METHOD FOR THE STUDY OF THE CIRCULATION

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A radiocardiogram is a tracing which graphically records the flow of blood through the heart. It is obtained in the following manner: A lead-shielded Geiger-Mueller tube with a small window in the shield is placed over the precordium. The tube in turn is connected to an especially designed ink-writing apparatus whose pen inscribes a line on moving graph paper. A small amount of radioactive sodium (Na^{24}, 0.01 to 0.02 mg.) in 3.0 c.c. of isotonic saline is injected into the antecubital vein. As the radioactive sodium arrives in the heart, the Geiger-Mueller tube transmits the impulses to the ink-writer which records a characteristic flow through the various phases of the cardiac cycle.

In patients with cardiac enlargement without failure, typical patterns are obtained which do not differ from patients with enlargement accompanied by failure. The probable significance of this will be discussed.

Preliminary studies on congenital heart disease reveal characteristic patterns in the tetralogy of Fallot and interventricular septal defects.

Circulation time, as routinely performed, is investigated by the use of radiocardiography. The influence of such extracardiac factors as volume injected, rapidity of injection, and temperature of the extremity is illustrated.

The rate of venous flow in the upper extremity as compared with that in the lower is easily demonstrated. The latter is shown to be markedly slower, thus explaining the predilection for thrombosis in this portion of the body.

Absorption studies are carried out by injecting Na^{24} intramuscularly and placing the Geiger-Mueller tube over the site of injection. Absorption is shown to be much slower than commonly believed and almost negligible in shock. The clinical importance of this is discussed.

STUDIES ON THE RELATIONSHIP OF DIET AND RENAL INSUFFICIENCY TO ARTERIAL DISEASE

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Arterial lesions involving large elastic arteries, muscular arteries, and arterioles have been produced with regularity in dogs by feeding a specified high fat diet for two months or longer, then experimentally inducing renal insufficiency in any one of several ways. The diet can be fed indefinitely and no lesions are ever observed unless the kidneys are damaged. Any time after two months of such a diet, kidney damage is regularly followed by arterial lesions. These lesions can be prevented or retarded by vitamin E, by cholesterol, or by simply omitting the high fat supplement for four weeks or longer.

From these experimental studies, the suspicion has grown that a disturbance of fatty acid metabolism is fundamental in the genesis of arterial lesions and that the kidney plays an important role in this disturbance. Chemical injury precedes anatomical change and both are conditioned by the pattern of lipid metabolism characteristic of the species. In some species, and possibly in all, cholesterol may be primarily protective and only secondarily alterative. These studies have further suggested that arterial disease may be a matter of days rather than decades, and that the effects of age may be more cumulative than causative.

FURTHER STUDIES ON THE PRODUCTION OF ARTERIOSCLEROSIS IN DOGS BY CHOLESTEROL AND THIOURACIL FEEDING

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It has been demonstrated (Steiner, A., and Kendall, F. E., Arch. Path. **42**: 433, 1946) that arteriosclerosis similar in distribution and morphologic characteristics to human arteriosclerosis develops in dogs following prolonged hypercholesterolemia produced by feeding 10 Gm. cholesterol daily when thyroid function is modified by thiouracil administration.

These results have been confirmed in a second series of experiments lasting twelve months upon dogs four months old at the beginning of the experiment. Extensive arteriosclerosis, including lesions in the cerebral vessels, was produced in both of the two dogs fed 10 Gm. of cholesterol and 1.0 Gm. of thiouracil each day. Minimal lesions were found in one of two dogs fed cholesterol alone and no lesions in three dogs given thiouracil alone. Studies are in progress to define more exactly the degree and duration of hypercholesterolemia required for the development of experimental arteriosclerosis in dogs.

SYMPATHECTOMY FOR ARTERIOSCLEROSIS OBLITERANS RATIONALE AND RESULTS

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Individuals suffering from the effects of obliterative arteriosclerosis of the peripheral vessels have long been thought to be beyond the reach of surgical aid as concerns measures designed to improve the circulation. This conclusion is not compatible with the experiences of several investigators who have performed lumbar sympathectomy in these patients.

The term arteriosclerosis obliterans is misleading if one presupposes that this implies inability of the smaller vessels to dilate. Despite marked organic involvement of the major vessels, the collateral and smaller vessels may be singularly uninvolved in many instances. Actually the major vessels are softer than normal rather than harder, except in areas where atheromatous plaques have become calcified. Permanent interruption of sympathetic impulses does not, insofar as we know, affect the major diseased vessels, but rather affords a more useful and extensive collateral blood supply through its effect on smaller vessels.

Sympathectomy affords a salvage in many instances so that the economic and physical liability following amputation is avoided. In our experience, the mortality following sympathectomy is less than 1.0 per cent. Even in the presence of established gangrene, arrest of the process is obtained in a worthwhile number of patients.

A few patients will not benefit from the procedure. These patients have been difficult to select and there is no uniformity of opinion among various authors regarding classification and selection of patients for the operation.

The salvage rate in eighty-three patients with advanced arteriosclerosis (Grades 3 and 4 of de Takats) subjected to sympathectomy at the University Hospital was over 70 per cent in a two-year follow-up.

Sympathectomy has proved to be a valuable prophylactic measure in patients with early symptomatic arteriosclerosis (intermittent claudication, night cramps, and cold extremities) and in patients with a single remaining lower extremity. At the Alexander Blain Hospital, patients in Groups 1 and 2 (de Takats) have been selected for operation since July, 1947. In all instances complete relief of symptoms has taken place.

More time will be necessary to evaluate the permanent effects in this series.

LUMBAR GANGLIONECTOMY IN PERIPHERAL ARTERIOSCLEROSIS

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The employment of lumbar ganglionectomy in the treatment of arteriosclerosis of the lower extremities has not enjoyed the acceptance that it has in other peripheral vascular diseases of obvious vasospastic character. The work of Flothow in 1931, using lumbar alcoholic injections began a series of studies by Robertson, Baker, Pearl, Atlas, Telford and Simmons, deTakats, Fowler, Jordan, and Risely which demonstrated the benefit of alleviating the arteriolospastic element in arteriosclerosis by interruption of the lumbar sympathetics.

Study of twenty-four patients with proved arteriosclerosis in the late stage in which minimal necrotic or gangrenous phenomena had occurred was carried out. The second and third lumbar sympathetic ganglia were removed through a muscle-splitting incision on a level with the tip of the twelfth rib.

Postoperative observation ranged from one month to forty-four months. Seventeen patients were improved, as evidenced by healing of the necrotic area after debridement or minimal amputation of a toe. The remaining eight patients were failures in which the gangrene progressed until supracondylar amputation became imperative. It was noted that the effect of sympathectomy did not disappear, but remained almost unchanged through the period of observation. Though sympathetic novocain block was employed preoperatively, it could not be depended on to indicate the expected effect of sympathectomy. The concomitant presence of diabetes in 46 per cent of the patients did not affect the results.

GLOMERULAR LIPOIDOSIS IN INTERCAPILLARY GLOMERULOSCLEROSIS

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Differential counts of the amount of lipid deposited in the glomeruli of twenty-one kidneys with intercapillary glomerulosclerosis were done on frozen sections stained with Sudan III. A statistically significantly larger amount of glomerular lipid was found than in comparable groups of twenty kidneys each of (a) arteriolar nephrosclerosis, (b) glomerulonephritis, (c) diabetes without hypertension, (d) diabetes with hypertension but without the renal lesion of intercapillary glomerulosclerosis, (e) miscellaneous renal lesions including several types of nephrosis, and (f) normal kidneys from persons of the same age span.

Not only did a larger percentage of all glomeruli from kidneys with intercapillary glomerulosclerosis contain lipid than in the control groups, but a larger number of kidneys with this lesion contained appreciable amounts of glomerular

lipid. Furthermore, the amount of glomerular lipid in intercapillary glomerulosclerosis was directly proportional to the severity of the renal lesion. This was not found to be the case in the control groups. Finally, distinctive features in the amount, form, and location of glomerular lipid deposits were noted in the group with intercapillary glomerulosclerosis.

These observations and the inferences drawn from them suggest that the deposition of fat in glomeruli is of primary importance in the development of the lesions of intercapillary glomerulosclerosis.

THE PREVENTION OF EXPERIMENTAL ATHEROSCLEROSIS BY CHOLINE FEEDINGS

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The oral feeding of 0.5 mg. choline chloride daily together with 0.5 Gm. cholesterol to twenty-nine three-month-old rabbits prevented atherosclerosis in 55 per cent of the animals at the expiration of the ninety-two day experimental period.

The oral feeding of 1.0 Gm. choline chloride daily together with 0.5 Gm. cholesterol to thirty-two three-month-old rabbits prevented atherosclerosis in 78 per cent at the expiration of the ninety-two day experimental period.

ABSORPTION OF AORTIC ATHEROSCLEROSIS BY CHOLINE FEEDING

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Choline caused reabsorption of aortic atherosclerosis in the majority of rabbits whose lesions had been produced by cholesterol feeding.

DISSECTING ANEURYSMS OF THE AORTA

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Fourteen cases of dissecting aneurysm of the aorta were reviewed from the morphologic and clinical aspect; two of these were on the basis of arteriosclerosis and twelve were secondary to medionecrosis of the aorta. Alterations were encountered in the vasa vasorum of nine aortas. Ischemia of the media of the aorta is implicated as the underlying primary factor in the production of medionecrosis. The various experimental, physiologic, anatomic, and congenital factors which may singly or in combination bring about medionecrosis and dissecting aneurysm are stressed. The vasa vasorum of the aorta in an instance of dissecting aneurysm were injected with radiopaque dye. The abnormal distribution of the vasa vasorum, as compared with the normal human aorta, is demonstrated.

NEW EXPERIMENTS IN ARTERIOSCLEROSIS

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A. Skeletal muscle suffers greatly in experimental cholesterol arteriosclerosis. There are two types of changes, not necessarily concomitant: (1) hyalinization, calcification, and nuclear proliferation in muscle fibers and (2) subendothelial lipoid cushions in arterioles. Guinea pigs are more gravely affected than rabbits. Denervation prior to cholesterol feeding prevents cholesterol damage. This seems to be a parallel to the findings of Pappenheimer; namely, that denervation prevents muscle damage by avitaminosis E.

B. The effect of stigmasterol on rabbits was studied to determine if it causes changes similar to cholesterol. This was tried on the grounds that stigmasterol is a phytosterol but resembles cholesterol in its formula. Moreover it does not change to any of the vitamins D. The results with feeding of stigmasterol (0.3 Gm. daily for 73 to 116 days) were negative.

C. In addition to rabbits and guinea pigs, golden hamsters also are susceptible to cholesterol arteriosclerosis. In contrast, rats are refractory. This may be explained by the fact that the latter are omnivores and readily dispose of the cholesterol. Recently, gophers were fed, for two to seven months, a milk-egg-yolk diet. None of these rodent herbivores showed cholesterol damage except cholesterol gallstones. Some foci of calcification were present, caused, perhaps, by the increased intake of vitamin D.

THE CLINICAL DIAGNOSIS OF ARTERIOSCLEROSIS WITH PARTICULAR REFERENCE TO THE USE OF THE ROENTGEN RAY

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No abstract.